

PEPTIDE ANTIANGIOGENIC DRUGS

Cross-Reference to Related Applications

5 This application is a continuation-in-part of U.S. Application Ser. No. 09/447,226, filed November 22, 1999, which is a continuation-in-part of U.S. Application Ser. No. 09/316,888, filed May 21, 1999, which claims priority to U.S. Provisional Application Ser. No. 60/126,546, filed March 26, 1999 and U.S. Provisional Application Ser. No. 60/086,536, filed May 22, 1998, all of which are incorporated herein by reference.

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The invention relates to novel compounds having activity useful for treating conditions which arise or are exacerbated by angiogenesis, pharmaceutical compositions comprising these compounds, a method of treating using said compounds, and a method of inhibiting angiogenesis.

Background of the Invention

20 Angiogenesis is the fundamental process by which new blood vessels are formed and is essential to a variety of normal body activities (such as reproduction, development and wound repair). Although the process is not completely understood, it is believed to involve a complex interplay of molecules which both stimulate and inhibit the growth of endothelial cells, the primary cells of the capillary blood vessels. Under normal conditions, these molecules appear to maintain the microvasculature in a quiescent state (i.e. one of no capillary growth) for prolonged periods which may last for as long as weeks or in some cases, decades. When necessary however (such as during wound repair), these same cells can undergo rapid proliferation and turnover within a five day period. (Folkman, J. and Shing, Y., *The Journal of Biological Chemistry*, **267**(16): 10931-10934, and Folkman, J. and Klagsbrun, M., *Science*, **235**: 442-447 (1987)).

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Although angiogenesis is a highly regulated process under normal conditions, many diseases (characterized as "angiogenic diseases") are driven by persistent unregulated angiogenesis. Otherwise stated, unregulated angiogenesis may either cause a particular disease directly or exacerbate an existing pathological condition. For example, ocular neovascularization has been implicated as the most common cause of blindness. In certain existing conditions such as arthritis, newly formed capillary blood vessels invade the joints and destroy cartilage. In diabetes, new capillaries formed in the retina invade the vitreous, bleed, and cause blindness. Growth and metastasis of solid tumors are also

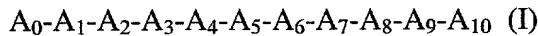
angiogenesis-dependent (Folkman, J., *Cancer Research*, **46**: 467-473 (1986), Folkman, J., *Journal of the National Cancer Institute*, **82**: 4-6 (1989)). It has been shown for example that tumors which enlarge to greater than 2 mm, must obtain their own blood supply and do so by inducing the growth of new capillary blood vessels. Once these new blood
5 vessels become embedded in the tumor, they provide a means for tumor cells to enter the circulation and metastasize to distant sites, such as liver, lung or bone (Weidner, N., et al., *The New England Journal of Medicine*, **324**(1): 1-8 (1991)).

Although several angiogenesis inhibitors are currently under development for use in treating angiogenic diseases (Gasparini, G. and Harris, A.L., *J Clin Oncol* **13**(3): 765-
10 782, (1995)), there are disadvantages associated with several of these compounds. For example, suramin is a potent angiogenesis inhibitor, but causes (at doses required to reach antitumor activity) severe systemic toxicity in humans. Other compounds, such as retinoids, interferons and antiestrogens are safe for human use but have only a weak anti-angiogenic effect.

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Summary of the Invention

In one aspect, the present invention provides a compound the formula of:



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or a pharmaceutically acceptable salt, ester, solvate, or prodrug thereof, wherein:

A_0 is hydrogen or an acyl group selected from:

- (1) $R-(\text{CH}_2)_n-\text{C}(\text{O})-$; wherein n is an integer from 0 to 8 and R is selected from hydroxyl; methyl; N-acetyl amino; methoxyl; carboxyl; cyclohexyl optionally containing a one or two double bonds and optionally substituted with one to three hydroxyl groups; and a 5- or 6-membered ring aromatic or nonaromatic ring optionally containing one or two heteroatoms selected from nitrogen, oxygen, and sulfur, wherein the ring is optionally substituted with a moiety selected from alkyl, alkoxy, and halogen; and
- (2) $R^1-\text{CH}_2\text{CH}_2-(\text{OCH}_2\text{CH}_2\text{O})_p-\text{CH}_2-\text{C}(\text{O})-$; wherein R^1 is selected from hydrogen, alkyl and N-acetyl amino, and p is an integer from 1 to 8;

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A_1 is an amino acyl residue selected from:

- (1) alanyl,
- (2) asparaginyl,

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- (3) citrullyl,
- (4) glutaminyl,
- (5) glutamyl,
- (6) N-ethylglycyl,
- (7) methionyl,
- (8) N-methylalanyl,
- (9) prolyl,
- (10) pyro-glutamyl,
- (11) sarcosyl,
- 10 (12) seryl,
- (13) threonyl,
- (14) -HN-(CH₂)_q-C(O)-, wherein q is 1 to 8, and
- (15) -HN-CH₂CH₂-(OCH₂CH₂O)_r-CH₂-C(O)-, wherein r is 1 to 8;

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A₂ is an amino acyl residue selected from:

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- (1) alanyl,
- (2) asparaginyl,
- (3) aspartyl,
- (4) glutaminyl,
- (5) glutamyl,
- 20 (6) leucyl,
- (7) methionyl,
- (8) phenylalanyl,
- (9) prolyl,
- (10) seryl,
- 25 (11) -HN-(CH₂)_q-C(O)-, wherein q is 1 to 8, and
- (12) -HN-CH₂CH₂-(OCH₂CH₂O)_r-CH₂-C(O)-, wherein r is 1 to 8;

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A₃ is an amino acyl residue selected from:

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- (1) alanyl,
- (2) asparaginyl,
- (3) citrullyl,
- (4) cyclohexylalanyl,
- (5) cyclohexylglycyl,
- (6) glutaminyl,
- (7) glutamyl,
- (8) glycyl,
- (9) isoleucyl,

(10)leucyl,
(11)methionyl,
(12)norvalyl,
5 (13)phenylalanyl,
(14)seryl,
(15)*t*-butylglycyl,
(16)threonyl,
(17)valyl,
10 (18)penicillaminy, and
(19)cystyl;

A₄ is an amino acyl residue of L or D configuration selected from:

(1) allo-isoleucyl,
(2) glycyl,
(3) isoleucyl,
15 (4) prolyl,
(5) dehydroleucyl,
(6) D-alanyl,
(7) D-3-(naphth-1-yl)alanyl,
(8) D-3-(naphth-2-yl)alanyl,
20 (9) D-(3-pyridyl)-alanyl,
(10)D-2-aminobutyryl,
(11)D-allo-isoleucyl,
(12)D-allo-threonyl;
(13)D-allylglycyl,
25 (14)D-asparaginyl,
(15)D-aspartyl,
(16)D-benzothienyl,
(17)D-3-(4,4'-biphenyl)alanyl,
(18)D-chlorophenylalanyl,
30 (19)D-3-(3-trifluoromethylphenyl)alanyl,
(20)D-3-(3-cyanophenyl)alanyl,
(21)D-3-(3,4-difluorophenyl)alanyl,
(22)D-citrullyl,
(23)D-cyclohexylalanyl,
35 (24)D-cyclohexylglycyl,
(25)D-cystyl,

(26)D-cystyl(*S-t*-butyl),
(27)D-glutaminyl,
(28)D-glutamyl,
(29)D-histidyl,
5 (30)D-homoisoleucyl,
(31)D-homophenylalanyl,
(32)D-homoseryl,
(33)D-isoleucyl,
(34)D-leucyl,
10 (35)D-lysyl(N-epsilon-nicotinyl),
(36)D-lysyl,
(37)D-methionyl,
(38)D-neopentylglycyl,
(39)D-norleucyl,
15 (40)D-norvalyl,
(41)D-ornithyl,
(42)D-penicillaminy1,
(43)D-penicillaminy1(acetamidomethyl),
(44)D-penicillaminy1(*S*-benzyl),
20 (45)D-phenylalanyl,
(46)D-3-(4-aminophenyl)alanyl,
(47)D-3-(4-methylphenyl)alanyl,
(48)D-3-(4-nitrophenyl)alanyl,
(49)D-3-(3,4-dimethoxyphenyl)alanyl,
25 (50)D-3-(3,4,5-trifluorophenyl)alanyl,
(51)D-prolyl,
(52)D-seryl,
(53)D-seryl(*O*-benzyl),
(54)D-*t*-butylglycyl,
30 (55)D-thienylalanyl,
(56)D-threonyl,
(57)D-threonyl(*O*-benzyl),
(58)D-tryptyl,
(59)D-tyrosyl(*O*-benzyl),
35 (60)D-tyrosyl(*O*-ethyl),
(61)D-tyrosyl, and

(62)D-valyl;

A₅ is an amino acyl residue of L or D configuration selected from:

- (1) alanyl,
- (2) (3-pyridyl)alanyl,
- 5 (3) 3-(naphth-1-yl)alanyl,
- (4) 3-(naphth-2-yl)alanyl,
- (5) allo-threonyl,
- (6) allylglycyl,
- 10 (7) glutaminyl,
- (8) glycyl,
- (9) histidyl,
- (10)homoseryl,
- (11)isoleucyl,
- (12)lysyl(N-epsilon-acetyl),
- 15 (13)methionyl,
- (14)norvalyl,
- (15{octylglycyl},
- (16)ornithyl,
- (17)3-(4-hydromethylphenyl)alanyl,
- 20 (18)prolyl,
- (19)seryl,
- (20)threonyl,
- (21)tryptyl,
- (22)tyrosyl,
- 25 (23)D-allo-threonyl,
- (24)D-homoseryl,
- (25)D-seryl,
- (26)D-threonyl,
- (27)penicillaminyl, and
- 30 (28)cystyl;

A₆ is an amino acyl residue of L or D configuration selected from:

- (1) alanyl,
- (2) 3-(naphth-1-yl)alanyl,
- (3) 3-(naphth-2-yl)alanyl,
- 35 (4) (3-pyridyl)alanyl,
- (5) 2-aminobutyryl,

(6) allylglycyl,
(7) arginyl,
(8) asparaginyl,
(9) aspartyl,
5 (10)citrullyl,
(11)cyclohexylalanyl,
(12)glutaminyl,
(13)glutamyl,
(14)glycyl,
10 (15)histidyl,
(16)homoalanyl,
(17)homoleucyl,
(18)homoseryl,
(19)isoleucyl,
15 (20)leucyl,
(21)lysyl(N-epsilon-acetyl),
(22)lysyl(N-epsilon-isopropyl),
(23)methionyl(sulfone),
(24)methionyl(sulfoxide),
20 (25)methionyl,
(26)norleucyl,
(27)norvalyl,
(28)octylglycyl,
(29)phenylalanyl,
25 (30)3-(4-carboxyamidephenyl)alanyl,
(31)propargylglycyl,
(32)seryl,
(33)threonyl,
(34)tryptyl,
30 (35)tyrosyl,
(36)valyl,
(37)D-3-(naphth-1-yl)alanyl,
(38)D-3-(naphth-2-yl)alanyl,
(39)D-glutaminyl,
35 (40)D-homoseryl,
(41)D-leucyl,

(42)D-norvalyl,
(43)D-seryl,
(44)penicillaminy1, and
(45)cystyl;

5 A₇ is an amino acyl residue of L or D configuration selected from:

(1) alanyl,
(2) allylglycyl,
(3) aspartyl,
(4) citrullyl,
10 (5) cyclohexylglycyl,
(6) glutamyl,
(7) glycyl,
(8) homoseryl,
(9) isoleucyl,
15 (10)allo-isoleucyl,
(11)leucyl,
(12)lysyl(N-epsilon-acetyl),
(13)methionyl,
(14)3-(naphth-1-yl)alanyl,
20 (15)3-(naphth-2-yl)alanyl,
(16)norvalyl,
(17)phenylalanyl,
(18)prolyl,
(19)seryl,
25 (20)*t*-butylglycyl,
(21)tryptyl,
(22)tyrosyl,
(23)valyl,
(24)D-allo-isoleucyl,
30 (25)D-isoleucyl,
(26)penicillaminy1, and
(27)cystyl;

A₈ is an amino acyl residue selected from:

(1) 2-amino-4-[(2-amino)-pyrimidinyl]butanoyl,
35 (2) alanyl(3-guanidino),
(3) alanyl[3-pyrrolidinyl(2-N-amidino)],

(4) alanyl[4-piperidinyl(N-amidino)],
(5) arginyl,
(6) arginyl($N^G N^{G'}$ diethyl),
(7) citrullyl,
5 (8) 3-(cyclohexyl)alanyl(4-N'-isopropyl),
(9) glycyl[4-piperidinyl(N-amidino)],
(10) histidyl,
(11) homoarginyl,
(12) lysyl,
10 (13) lysyl(N-epsilon-isopropyl),
(14) lysyl(N-epsilon-nicotinyl),
(15) norarginyl,
(16) ornithyl(N-delta-isopropyl),
(17) ornithyl(N-delta-nicotinyl),
15 (18) ornithyl[N-delta-(2-imidazolinyl)],
(19) [4-amino(N-isopropyl)methyl]phenyl]alanyl,
(20) 3-(4-guanidinophenyl)alanyl, and
(21) 3-(4-amino-N-isopropylphenyl)alanyl;

A₉ is an amino acyl residue of L or D configuration selected from:

20 (1) 2-amino-butyryl,
(2) 2-amino-isobutyryl,
(3) homoprolyl,
(4) hydroxyprolyl,
(5) isoleucyl,
25 (6) leucyl,
(7) phenylalanyl,
(8) prolyl,
(9) seryl,
(10) *t*-butylglycyl,
30 (11) 1,2,3,4-tetrahydroisoquinoline-3-carbonyl,
(12) threonyl,
(13) valyl,
(14) D-alanyl, and
(15) D-prolyl; and

35 A₁₀ is a hydroxyl group or an amino acid amide is selected from:

(1) azaglycylamide,

- (2) D-alanyl amide,
- (3) D-alanyl ethyl amide,
- (4) glycyl amide,
- (5) glycyl ethyl amide,
- (6) sarcosyl amide,
- (7) seryl amide,
- (8) D-seryl amide,
- (9) a group represented by the formula

(9) a group represented by the formula $\text{-NH-}\overset{\text{R}^2}{\underset{\text{I}}{\text{C}}}\text{-}\overset{\text{R}^3}{\text{H}}$; and

wherein:

s is an integer selected from 0 to 8,

R^2 is selected from hydrogen, alkyl, and a 5- to 6-membered cycloalkyl

ring;

R^3 is selected from hydrogen, hydroxy, alkyl, phenyl, alkoxy, and a 5- to 6-membered ring optionally containing from one to two heteroatoms selected from oxygen, nitrogen, and sulfur, provided that s is not zero when R^3 is hydroxy or alkoxy; and

R^4 is selected from hydrogen, hydroxy, and a 5- to 6-membered cycloalkyl ring.

In another aspect, the present invention provides a composition for treating a patient in need of anti-angiogenesis therapy comprising a peptide defined above in combination with a pharmaceutically acceptable carrier.

Yet another aspect of the present invention provides a method for treating a patient
in need of anti-angiogenesis therapy comprising administering to the patient a
therapeutically effective amount of a peptide as defined above.

Still yet another aspect of the present invention provides a composition for the treatment of a disease selected from cancer, arthritis, psoriasis, angiogenesis of the eye associated with infection or surgical intervention, macular degeneration and diabetic retinopathy comprising a peptide as defined above in combination with a pharmaceutically acceptable carrier.

In yet another aspect, the present invention provides a method of isolating a receptor from an endothelial cell comprising binding a peptide as defined above to the receptor to form a peptide receptor complex, isolating the peptide receptor complex, and purifying the receptor.

In another aspect, the present invention provides a compound of formula (II)



(II),

or a pharmaceutically acceptable salt, ester, prodrug, or solvate thereof, wherein

5 AA³ is selected from the group consisting of

- (1) glutaminy1,
- (2) phenylalanyl,
- (3) valyl, and
- (4) asparaginyl;

10 AA⁴ is selected from the group consisting of

- (1) D-isoleucyl,
- (2) isoleucyl,
- (3) D-leucyl, and
- (4) D-alloisoleucyl;

15 AA⁵ is selected from the group consisting of

- (1) seryl,
- (2) methionyl,
- (3) allothreonyl,
- (4) threonyl, and
- (5) tyrosyl;

20 AA⁶ is selected from the group consisting of

- (1) norvalyl,
- (2) seryl,
- (3) tryptophyl,
- (4) glutaminy1, and
- (5) prolyl;

25 AA⁷ is selected from the group consisting of

- (1) isoleucyl,
- (2) D-isoleucyl,
- (3) lysyl(acetyl), and
- (4) prolyl; and

30 AA¹⁰ is selected from the group consisting of

- (1) D-alanyl amide,
- (2) ethylamide, and
- (3) isopropylamide;

35 with the proviso that at least one of AA⁴, AA⁷, and AA¹⁰ is a D-amino acid.

In another aspect, the present invention provides a pharmaceutical composition comprising a compound of formula (II), or a pharmaceutically acceptable salt, ester, prodrug, or solvate thereof, and a pharmaceutically acceptable carrier.

In another aspect, the present invention provides a method of treating a patient in need of anti-angiogenesis therapy comprising administering to the patient in need a therapeutically effective amount of a compound of formula (II), or a pharmaceutically acceptable salt, ester, prodrug, or solvate thereof.

In another aspect, the present invention provides a composition for the treatment of a disease selected from cancer, arthritis, psoriasis, angiogenesis of the eye associated with infection or surgical intervention, macular degeneration and diabetic retinopathy comprising a compound of formula (II), or a pharmaceutically acceptable salt, ester, prodrug, or solvate thereof, in combination with a pharmaceutically acceptable carrier.

In another aspect, the present invention provides a method of isolating a receptor from an endothelial cell comprising binding a compound of formula (II), or pharmaceutically acceptable salt, ester, prodrug, or solvate thereof, to the receptor to form a peptide receptor complex; isolating the peptide receptor complex; and purifying the receptor.

Detailed Description of the Invention

Definition of Terms

The term "alkyl" as used herein refers to a monovalent group derived from a straight or branched chain saturated hydrocarbon by the removal of a hydrogen atom. Examples of alkyl include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, pentyl, hexyl, and the like. Preferred alkyl groups for the invention are C₁-C₆ alkyl groups having from one to six carbon atoms. Alkyl groups of one to three carbon atoms (C₁-C₃ alkyl) are more preferred for the invention.

The term "nicotinyl" as used herein refers to the acyl group derived from nicotinic acid, i.e. pyridine-3-carboxylic acid. The term "2-Me-nicotinyl" or "2-methylnicotinyl" refers to a nicotinyl moiety substituted with a methyl group at the carbon adjacent to the nitrogen atom in the 2-position. The term "6-Me-nicotinyl" or "6-methylnicotinyl" refers to a nicotinyl moiety substituted with a methyl group at the carbon adjacent to the nitrogen atom in the 6-position.

The term "shikimyl" as used herein refers to the acyl residue derived from shikimic acid or [3R-(3 α ,4 α ,5 β)-3,4,5-trihydroxy]-1-cyclohexene-1-carboxylic acid. A "dihydroshikimyl" group denotes the fully saturated analog of shikimic acid.

The term "succinyl" as used herein refers to the acyl residue derived from succinic acid or (1,4-dioxobutyl)-1-carboxylic acid.

The term "N-acetylamino" as used herein refers to an amino moiety (-NH₂) substituted on the nitrogen atom with an acetyl (CH₃C(O)-) group.

5 The term "carbonyl" as used herein refers to the group -C(O)-.

The term "carboxy" or "carboxyl" as used herein refers to the group -C(O)OH.

The term "alkoxy" as used herein refers to an alkyl group as defined above attached to a parent molecular moiety via an ether linkage. Exemplary alkoxy groups include, but are not limited to, methoxy, ethoxy, isopropoxy, and the like.

10 The term "aromatic ring" as used herein refers to an unsaturated cyclic hydrocarbon associated with a system of π-electron bonds. One to two carbon atoms of the hydrocarbon ring can be substituted with a heteroatom selected from nitrogen, oxygen, or sulfur. Exemplary 5- or 6-membered aromatic rings include, but are not limited to, benzyl, pyridyl, furyl, tetrahydrofuryl, thienyl, and pyrrolyl. An aromatic ring, including rings
15 substituted with a heteroatom, can be optionally substituted on one or more carbon atoms with substituents selected from alkyl, alkoxy, carboxy, and halogen, for example, tolyl, bromobenzyl, *t*-butylbenzyl, nicotinyl, 2-methylnicotinyl, 2-furoic acid, and the like.

20 The term "nonaromatic ring" as used herein refers to a saturated or unsaturated cyclic hydrocarbon ring, which can be optionally substituted with one or two heteroatoms selected from nitrogen, oxygen, or sulfur. Exemplary nonaromatic rings are cyclohexyl, tetrahydropyranyl, pyrrolidinyl, and piperidinyl.

25 The term "N-protecting group" as used herein refers to an easily removable group which is known in the art to protect an amino group against undesirable reaction during synthetic procedures and to be selectively removable. The use of N-protecting groups is well known in the art for protecting groups against undesirable reactions during a synthetic procedure and many such protecting groups are known, cf, for example, T.H. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 2nd edition, John Wiley & Sons, New York (1991). Examples of N-protecting groups include, but are not limited to, acyl groups including acetyl, trifluoroacetyl, acylisothiocyanate, aminocaproyl, benzoyl and the like, and acyloxy groups, including *t*-butyloxycarbonyl (Boc) and carbobenzyloxy (Cbz), 9-fluorenylmethoxycarbonyl (Fmoc), and the like.

30 As used herein the terms "Leu," "Sar," "Gln," "Gly," "Val," "Ile," "Thr," "Nva," "Arg," "Asn," "pyroGlu," "Ser," "Ala," "Homoala," "Cha," "Pro," "Phe," "Trp," "1-Nal," "2-Nal," "Azagly" and "Nle" refer to leucine, sarcosine (N-methylglycine), glutamine, glycine, valine, isoleucine, threonine, norvaline, arginine, asparagine, pyroglutamic acid, serine, alanine, homoalanine, cyclohexylalanine, proline, phenylalanine, tryptophan, 1-

naphthylalanine, 2-naphthylalanine, azaglycine, and norleucine, respectively, in their L-, D- or DL forms. Unless indicated otherwise by a "D" prefix, e.g. D-Ala or D-Ile (also D-Ile), the stereochemistry of the α -carbon of the amino acids and aminoacyl residues in peptides described in this specification and the appended claims is the natural or "L" configuration. The Cahn-Ingold-Prelog "R" and "S" designations are used to specify the stereochemistry of chiral centers in certain of the acyl substituents at the N-terminus of the peptides of this invention. The designation "R,S" is meant to indicate a racemic mixture of the two enantiomeric forms. This nomenclature follows that described in R.S. Cahn, *et al.*, *Angew. Chem. Int. Ed. Engl.*, **5**, 385-415 (1966).

For the most part, the names on naturally occurring and non-naturally occurring aminoacyl residues used herein follow the naming conventions suggested by the IUPAC Commission on the Nomenclature of Organic Chemistry and the IUPAC-IUB Commission on Biochemical Nomenclature as set out in "Nomenclature of α -Amino Acids (Recommendations, 1974)" *Biochemistry*, 14(2), (1975). To the extent that the names and abbreviations of amino acids and aminoacyl residues employed in this specification and appended claims differ from those suggestions, they will be made clear to the reader. Some abbreviations useful in describing the invention are defined below in the following Table 1.

Table 1

<u>Abbreviation</u>	<u>Definition</u>
Abu	2-aminobutyric acid
6-Ac-Aca	6-NAc-caproyl, 6-N-Ac-(CH ₂) ₅ C(O)-, or 6-N-acetyl-aminocaproic acid
N-Ac-Sar	N-acetylsarcosyl
Aib	2-aminoisobutyric acid
Ala(3-guanidino)	alanine(3-guanidino)
AlaNH ₂	alanylamide
Ala(3-pyrrolidinylamidino)	alanine[3-pyrrolidinyl(2-N-amidino)]
Ala[4-Pip(N-amidino)]	alanine[4-piperidinyl(N-amidino)]
alloIle	alloisoleucyl
alloThr	allothreonyl
alloThr(tBu)	allothreonyl(<i>O</i> - <i>tert</i> -butyl)
Allylgly	2-(allyl)glycine
AM	aminomethyl
Aminopyrimidinobutanoyl	2-amino-4-[(2-amino)pyrimidinyl]butanoic acid

Asn(trt)	asparagine(N-trityl)
Azagly	azaglycine
3-Ac-Bala	3-N-acetyl-beta-alanine
Bala	beta-alanine
Cha	3-(cyclohexyl)alanine
Cha(4-NIsp)	3-(cyclohexyl)alanine(4-N'-isopropyl)
Cit	citrulline
2ClTrt	2-chloro-trityl

Table 1 (continued)

Cys(tBu)	cysteine(S-t-butyl)
D-2-Thienylala	D-3-(2-thienyl)alanine
D-3,3-Diphenylala	D-3,3-(diphenyl)alanine
D-3,4-diClPhe	D-3-(3,4-dichlorophenyl)alanine
D-3,4-diFPhe	D-3-(3,4-difluorophenyl)alanine
D-3-Benzothienylala	D-3-(3-benzothienyl)alanine
D-3-CF ₃ Phe	D-3-(3-trifluoromethylphenyl)alanine
D-3-ClPhe	D-3-(3-chlorophenyl)alanine
D-3-CNphe	D-3-(3-cyanophenyl)alanine
D-3-Pal	D-(3-pyridyl)alanine
D-4,4'-Biphenylala	D-3-(4,4'-biphenyl)alanine
D-4-ClPhe	D-3-(4-chloro-phenyl)alanine
D-Cha	D-3-(cyclohexyl)alanine
D-Chg	D-cyclohexylglycine
Dehydroleu	dehydroleucine
D-Hphe	D-homophenylalanine
D-Ile	D-isoleucine
D-alloIle	D-allo-isoleucine
D-Lys(Nic)	D-lysine(N-epsilon-nicotinyl)
D-Leu	D-leucine
D-pentaFPhe	D-3-(pentafluorophenyl)alanine
D-Val	D-valine
4-Ac-Gaba	4-N-acetyl-gamma-aminobutyric acid or 4-N-acetyl-4-aminobutyric acid
Gaba	gamma-aminobutyric acid or 4-aminobutyric acid
Gln(trt)	glutamine(N-trityl)

Gly[4-Pip(N-amidino)]	glycine[4-piperidinyl(N-amidino)]
Harg	homoarginine
Hle	homoleucine
Hser	homoserine
Hyp	4-hydroxyproline
Isp	isopropyl
Lys(Ac)	lysine(N-epsilon-acetyl)
Lys(Isp)	lysine(N-epsilon-isopropyl)

Table 1 (continued)

Lys(Nic)	lysine(N-epsilon-nicotinyl)
Met(O)	methionine sulfoxide
Met(O ₂)	methionine sulfone
MeOAc or (MeO)acetyl	methoxyacetyl
1Nal	3-(naphth-1-yl)alanine
2Nal	3-(naphth-2-yl)alanine
N-Ac-Sar	N-acetylsarcosine
Neopentylgly	neopentylglycine
NEtGly	N-ethylglycine
Norarg	norarginine
Octylgly	2-(octyl)glycine
Orn(Ac)	ornithine(N-delta-acetyl)
Orn(2-imidazo)	ornithine [N-delta-(2-imidazolinyl)]
Orn(Isp)	ornithine(N-delta-isopropyl)
Orn(Nic)	ornithine(N-delta-nicotinyl)
O-TBDMS	<i>O</i> - <i>t</i> -butyldimethylsilyl
Pen	penicillamine or β,β -dimethylcysteine
Pen(Acm)	penicillamine(acetamidomethyl)
D-Phe(3,4,5-triF)	D-3-(3,4,5-trifluorophenyl)alanine
D-Phe(3,4-diMeO)	D-3-(3,4-dimethoxyphenyl)alanine
Phe(4-CH ₂ OH)	3-(4-hydroxymethylphenyl)alanine
Phe(4-CONH ₂)	3-(4-carboxyamidephenyl)alanine
Phe(4-guanidino)	3-(4-guanidinophenyl)alanine
D-Phe(4-Me)	D-3-(4-methylphenyl)alanine

D-Phe(4-NH ₂)	D-3-(4-aminophenyl)alanine
Phe(4-NIsp)	3-(4-amino-N-isopropylphenyl)alanine

Table 1 (continued)

Phe(4-CH ₂ NHIsop)	[(4-amino(N-isopropyl)methyl)phenyl]alanine
D-Phe(4-NO ₂)	D-3-(4-nitrophenyl)alanine
Propargylgly	propargylglycine
Pip	pipecolic acid or homoproline
pyBrop	bromo-tris-pyrrolidinophosphoniumhexafluorophosphate
Ser(tBu)	serine(<i>O</i> - <i>tert</i> -butyl)
Ser(Bzl)	serine(<i>O</i> -benzyl)
tButylgly	<i>t</i> -butylglycine
Thr(t-Bu)	threonine (<i>O</i> - <i>tert</i> -butyl)
Thr(Bzl)	threonine(<i>O</i> -benzyl)
Tic	1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid
Trp(Boc)	tryptophan(<i>N</i> - <i>tert</i> -butoxycarbonyl)
Trt	trityl
Tyr(tBu)	tyrosine(<i>O</i> - <i>tert</i> -butyl)
Tyr(Bzl)	tyrosine(<i>O</i> -benzyl)
Tyr(Et)	tyrosine(<i>O</i> -ethyl)
THF	tetrahydrofuryl or tetrahydrofuran
2-THFcarbonyl	(tetrahydro-2-furyl)carbonyl

When not found in the table above, nomenclature and abbreviations may be further
 5 clarified by reference to the Calbiochem-Novabiochem Corp. 1999 *Catalog and Peptide Synthesis Handbook* or the Chem-Impex International, Inc. *Tools for Peptide & Solid Phase Synthesis 1998-1999 Catalogue*.

The term "pharmaceutically acceptable salt" as used herein refers to salts which
 are, within the scope of sound medical judgement, suitable for use in contact with the
 10 tissues of humans and lower animals without undue toxicity, irritation, allergic response
 and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically
 acceptable salts are well known in the art . For example, S. M. Berge, *et al.* describe
 pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 1977, 66: 1-19.
 The salts can be prepared *in situ* during the final isolation and purification of the
 15 compounds of the invention, or separately by reacting the free base function with a

suitable organic acid. Representative acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphersulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, 5 hexanoate, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate, undecanoate, valerate salts, and 10 the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like.

15 As used herein, the term "pharmaceutically acceptable ester" refers to esters which hydrolyze *in vivo* and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanoic, alkenoic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety 20 advantageously has not more than 6 carbon atoms. Examples of particular esters include formates, acetates, propionates, butyrates, acrylates and ethylsuccinates.

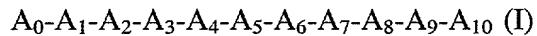
The term "pharmaceutically acceptable solvate" represents an aggregate that comprises one or more molecules of the solute, such as a formula (I) compound, with one or more molecules of solvent.

25 The term "pharmaceutically acceptable prodrugs" as used herein refers to those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals with undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the 30 zwitterionic forms, where possible, of the compounds of the invention. The term "prodrug" refers to compounds that are rapidly transformed *in vivo* to yield the parent compound of the above formula, for example by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible 35 Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

The term "receptor" as used herein refers to a chemical group or molecule on the cell surface or in the cell interior that has an affinity for a specific chemical group, molecule, or virus. Isolation of receptors relevant to the antiangiogenic activity of the peptide of the invention can provide useful diagnostic tools.

5

In one embodiment, the present invention relates to compounds of the structure



wherein A_0 , A_1 , A_2 , A_3 , A_7 , A_8 , A_9 , and A_{10} are as defined above. The N-terminus of a nonapeptide represented by A_1-A_9 can be modified by an amino acyl group represented by

10 A_0 . A_{10} represents a group suitable for modifying the C-terminus of the compound.

In the present embodiment, A_4 is an amino acyl residue having a D configuration selected from D-allo-isoleucyl, D-allylglycyl, D-3-(3-cyanophenyl)alanyl, D-cystyl, D-isoleucyl, D-leucyl, D-penicillaminy, D-phenylalanyl, D-3-(3,4,5-trifluorophenyl)alanyl, and D-3-(4-aminophenyl)alanyl; A_5 is an amino acyl residue selected from octylglycyl, 15 glycyl, penicillaminy, seryl, threonyl, and tyrosyl; and A_6 is an amino acyl residue selected from glutaminy, leucyl, norvalyl, and seryl.

In another embodiment of the invention, the compounds have the structure (I) as defined above wherein A_1 is sarcosyl, A_2 is glycyl, A_3 is valyl, A_7 is isoleucyl, A_8 is arginyl, and A_9 is prolyl. Compounds of the present embodiment can be represented by 20 the structure



wherein A_0 is hydrogen or an acyl group modifying the N-terminus. Suitable groups for A_0 can be represented by the formula $R\text{-(CH}_2\text{)}_n\text{C(O)-}$; wherein n is an integer from 0 to 8 and R is selected from hydroxyl; methyl; N-acetylamino; methoxyl; carboxyl; cyclohexyl 25 optionally containing a one or two double bonds and optionally substituted with one to three hydroxyl groups; and a 5- or 6-membered ring aromatic or nonaromatic ring optionally containing one or two heteroatoms selected from nitrogen, oxygen, and sulfur, wherein the ring is optionally substituted with a moiety selected from alkyl, alkoxy, and halogen; or $R^1\text{-CH}_2\text{CH}_2\text{-(OCH}_2\text{CH}_2\text{O)}_p\text{-CH}_2\text{-C(O)-}$; wherein R^1 is selected from hydrogen, 30 alkyl, and N-acetylamino, and p is an integer from 1 to 8.

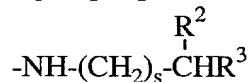
A_4 is an amino acyl residue of L or D configuration selected from allo-isoleucyl, dehydroleucyl, glycyl, isoleucyl, prolyl, D-alanyl, D-3-(naphth-1-yl)alanyl, D-3-(naphth-2-yl)alanyl, D-(3-pyridyl)-alanyl, D-2-aminobutyryl, D-allo-isoleucyl, D-allo-threonyl, D-allylglycyl, D-asparaginyl, D-aspartyl, D-benzothienyl, D-3-(4,4'-biphenyl)alanyl, D-chlorophenylalanyl, D-3-(3-trifluoromethylphenyl)alanyl, D-3-(3-cyanophenyl)alanyl, D-3-(3,4-difluorophenyl)alanyl, D-citrullyl, D-cyclohexylalanyl, D-cyclohexylglycyl, D-

cystyl, D-cystyl(*S*-*t*-butyl), D-glutaminyl, D-glutamyl, D-histidyl, D-homoisoleucyl, D-homophenylalanyl, D-homoseryl, D-isoleucyl, D-leucyl, D-lysyl(N-epsilon-nicotinyl), D-lysyl, D-methionyl, D-neopentylglycyl, D-norleucyl, D-norvalyl, D-ornithyl, D-penicillaminyl, D-penicillaminyl(acetamidomethyl), D-penicillaminyl(*S*-benzyl), D-phenylalanyl, D-3-(4-aminophenyl)alanyl, D-3-(4-methylphenyl)alanyl, D-3-(4-nitro-phenyl)alanyl, D-3-(3,4-dimethoxyphenyl)alanyl, D-3-(3,4,5-trifluorophenyl)alanyl, D-prolyl, D-seryl, D-seryl(*O*-benzyl), D-*t*-butylglycyl, D-thienylalanyl, D-threonyl, D-threonyl(*O*-benzyl), D-tryptyl, D-tyrosyl(*O*-benzyl), D-tyrosyl(*O*-ethyl), D-tyrosyl, and D-valyl.

10 A₅ is an amino acyl residue of L or D configuration selected from alanyl, (3-pyridyl)-alanyl, 3-(naphth-1-yl)alanyl, 3-(naphth-2-yl)alanyl, allo-threonyl, allylglycyl, glutaminyl, glycyl, histidyl, homoseryl, isoleucyl, lysyl(N-epsilon-acetyl), methionyl, norvalyl, octylglycyl, ornithyl, 3-(4-hydroxymethylphenyl)alanyl, prolyl, seryl, threonyl, tryptyl, tyrosyl, D-allo-threonyl, D-homoseryl, D-seryl, D-threonyl, penicillaminyl, and cystyl.

15 A₆ is an amino acyl residue of L or D configuration selected from alanyl, 3-(naphth-1-yl)alanyl, 3-(naphth-2-yl)alanyl, (3-pyridyl)alanyl, 2-aminobutyryl, allylglycyl, arginyl, asparaginyl, aspartyl, citrullyl, cyclohexylalanyl, glutaminyl, glutamyl, glycyl, histidyl, homoalanyl, homoleucyl, homoseryl, isoleucyl, leucyl, lysyl(N-epsilon-acetyl), lysyl(N-epsilon-isopropyl), methionyl(sulfone), methionyl(sulfoxide), methionyl, norleucyl, norvalyl, octylglycyl, phenylalanyl, 3-(4-carboxyamidephenyl)alanyl, propargylglycyl, seryl, threonyl, tryptyl, tyrosyl, valyl, D-3-(naphth-1-yl)alanyl, D-3-(naphth-2-yl)alanyl, D-glutaminyl, D-homoseryl, D-leucyl, D-norvalyl, D-seryl, penicillaminyl, and cystyl.

20 A₁₀ is a hydroxyl group or an amino acid amide selected from azaglycylamide, D-alanyl amide, D-alanylethylamide, glycylamide, glycylethylamide, sarcosylamide, seryl amide, D-seryl amide, or A₁₀ is a group represented by the formula



25 or a group represented by the formula -NH-R⁴, wherein s is an integer selected from 0 to 8; R² is selected from hydrogen, alkyl, and a 5- to 6-membered cycloalkyl ring; R³ is selected from hydrogen, hydroxy, alkyl, phenyl, alkoxy, and a 5- to 6-membered ring optionally containing from one to two heteroatoms selected from oxygen, nitrogen, and sulfur, provided that s is not zero when R³ is hydroxy or alkoxy; and R⁴ is selected from hydrogen, hydroxy, and a 5- to 6-membered cycloalkyl ring.

Preferred compounds of the invention have the structure (III) as defined above, wherein A₄ is an amino acyl residue having a D configuration selected from D-alanyl, D-3-(naphth-1-yl)alanyl, D-3-(naphth-2-yl)alanyl, D-(3-pyridyl)-alanyl, D-2-aminobutyryl, D-allo-isoleucyl, D-allo-threonyl, D-allylglycyl, D-asparaginyl, D-aspartyl, D-chlorophenylalanyl, D-3-(3-trifluoromethylphenyl)alanyl, D-3-(3-cyanophenyl)alanyl, D-3-(3,4-difluorophenyl)alanyl, D-cyclohexylalanyl, D-cyclohexylglycyl, D-cystyl, D-glutaminyl, D-glutamyl, D-histidyl, D-homoisoleucyl, D-homophenylalanyl, D-homoseryl, D-isoleucyl, D-leucyl, D-lysyl(N-epsilon-nicotinyl), D-methionyl, D-neopentylglycyl, D-norleucyl, D-norvalyl, D-penicillaminyl, D-penicillaminyl(acetamidomethyl), D-penicillaminyl(S-benzyl), D-phenylalanyl, D-3-(4-aminophenyl)alanyl, D-3-(4-methylphenyl)alanyl, D-3-(4-nitrophenyl)alanyl, D-3-(3,4-dimethoxyphenyl)alanyl, D-3-(3,4,5-trifluorophenyl)alanyl, D-prolyl, D-seryl, D-seryl(O-benzyl), D-t-butylglycyl, D-thienylalanyl, D-threonyl, D-threonyl(O-benzyl), D-tyrosyl(O-ethyl), D-tyrosyl, D-valyl, and D-cystyl.

Other preferred compounds of the present invention have the structure of formula (III), wherein A₅ is selected from glycyl, octylglycyl, penicillaminyl, seryl, threonyl, and tyrosyl.

Additional preferred compounds of the present invention have the structure represented by formula (III), wherein A₆ is selected from glutaminyl, leucyl, norvalyl, and seryl.

The more preferred amino acid residues for substituting the position represented by A₄ are D configuration amino acids selected from D-allo-isoleucyl, D-allylglycyl, D-3-(3-cyanophenyl)alanyl, D-cystyl, D-isoleucyl, D-leucyl, D-penicillaminyl, D-phenylalanyl, D-3-(3,4,5-trifluorophenyl)alanyl, and D-3-(4-aminophenyl)alanyl.

Preferred A₀ groups for modifying the N-terminus of the compounds in the scope of the invention are selected from acetyl, butyryl, caproyl, (4-N-acetylamino)butyryl, N-acetyl-beta-alanyl, (6-N-acetylamino)caproyl, chloronicotinyl, cyclohexylacetyl, furoyl, gamma-aminobutyryl, 2-methoxyacetyl, methylnicotinyl, nicotinyl, (8-N-acetylamino)-3,6-dioxo-octanoyl, phenylacetyl, propionyl, shikimyl, succinyl, and tetrahydrofuroyl.

The preferred A₁₀ groups for modifying the C-terminus of the invention are selected from D-alanylamide, azaglycylamide, serylamide, ethylamide, hydroxylamide, isopropylamide, propylamide, 2-(cyclohexyl)ethylamide, 2-(1-pyrrolidine)ethylamide, 1-(cyclohexyl)ethylamide, 2-(methoxy)ethylamide, 2-(hydroxy)ethylamide, 2-(2-pyridine)ethylamide, (2-pyridine)methylamide, 2-(3-pyridine)ethylamide, 2-(2-(1-methyl)pyrrolidine)ethylamide, 2-(N-morpholine)ethylamide, and cyclopropylmethylamide.

Compounds contemplated as falling within the scope of the present invention include, but are not limited to:

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
5 pyroGlu-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH(CH₃)₂,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₂-(1-pyrrolidine),
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHethylpiperidine,
10 N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHmethylcyclopropyl,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNH(ethyl-1-(R)-cyclohexyl),
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNH₂,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₂OCH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₂cyclohexyl,
15 N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH(CH₃)₂,
N-Ac-Sar-Gly-Val-D-alloIle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-Gly-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
20 N-Ac-Sar-Gly-Val-D-Val-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ala-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Met-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Nle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Phe-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
25 N-Ac-Sar-Gly-Val-D-Tyr-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-4,4'-Biphenylala-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Cha-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Chg-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-4-ClPhe-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
30 N-Ac-Sar-Gly-Val-D-Hphe-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-Dehydroleu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-3-CF₃Phe-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-pentaFPhe-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-3,4-diClPhe-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
35 N-Ac-Sar-Gly-Val-D-3-ClPhe-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-2-Thienylala-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,

N-Ac-Sar-Gly-Val-D-3-CNPhe-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-DNva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Cha-Ile-Arg-ProNHCH₂CH₃,
5 N-Ac-Sar-Gly-Val-D-Ile-Thr-Gly-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Ala-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Val-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Abu-Ile-Arg-ProNHCH₂CH₃
N-Ac-Sar-Gly-Val-D-Ile-Thr-Allylgly-Ile-Arg-ProNHCH₂CH₃,
10 N-Ac-Sar-Gly-Val-D-Ile-Thr-Octylgly-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Met-Ile-Arg-ProNHCH₂CH₃,
N-Cyclohexylacetyl-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-(2-Me-Nicotinyl)-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Succinyl-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
15 N-Nicotinyl-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Propionyl-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-(MeO)acetyl-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-(Shikimyl)-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-(2-Furoyl)-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
20 N-Butyryl-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N(2-THFcarbonyl)-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-[CH₃CONH-(CH₂)₂-O-(CH₂)₂-O-CH₂-C(O)]-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-
Arg-ProNHCH₂CH₃

25 N[6-N-acetyl-(CH₂)₅C(O)]-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Hexanoyl-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-[4-N-Acetylaminobutyryl]-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
H-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Asn-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
30 N-[CH₃C(O)NH-(CH₂)₂-O-(CH₂)₂-O-CH₂-C(O)]-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-
ProNHCH₂CH₃,

N-Ac-Pro-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Gly-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
35 N-Ac-Ala-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-NEtGly-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,

N-Ac-Sar-Gly-Val-D-Ile-Thr-Leu-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Ser-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Pro-D-AlaNH₂
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-D-ProNHCH₂CH₃,
5 N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-AbuNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Phe-NHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Tic-NHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Hyp-NHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Aib-NHCH₂CH₃,
10 N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-D-Ala-NHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Pip-NHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Tyr(Et)-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Cys(tBu)-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Cys-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
15 N-Ac-Sar-Gly-Val-D-Tyr(Bzl)-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ser(Bzl)-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-1Nal-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-tButylgly-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Orn-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
20 N-Ac-Sar-Gly-Val-D-Thr(Bzl)-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-2Nal-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Phe(4-Me)-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Phe-(3,4-diMeO)-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Phe(3,4,5-triF)-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
25 N-Ac-Sar-Gly-Val-D-(4-NO₂)Phe-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Pen-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Pen(Acm)-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Abu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Phe(4-NH₂)-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
30 N-Ac-Sar-Gly-Val-D-Leu-Thr-Nva-Ala-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Leu-Thr-Nva-Met-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Leu-Thr-Nva-Phe-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Leu-Thr-Nva-Tyr-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Leu-Thr-Nva-Nva-Arg-ProNHCH₂CH₃,
35 N-Ac-Sar-Gly-Val-D-Leu-Thr-Nva-Asp-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Leu-Thr-Nva-Gly-Arg-ProNHCH₂CH₃,

N-Ac-Sar-Gly-Val-D-Leu-Thr-Nva-Lys(Ac)-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Leu-Thr-Nva-Leu-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Leu-Thr-Nva-2Nal-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Leu-Thr-Nva-1Nal-Arg-ProNHCH₂CH₃,
5 N-Ac-Sar-Gly-Val-D-Leu-Thr-Nva-Allylgly-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Leu-Thr-Nva-Cit-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Leu-Ala-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Leu-Pro-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Leu-Trp-Nva-Ile-Arg-ProNHCH₂CH₃,
10 N-Ac-Sar-Gly-Val-D-Leu-Tyr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Leu-Nva-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Leu-Gly-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Leu-Lys(Ac)-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Leu-2Nal-Nva-Ile-Arg-ProNHCH₂CH₃,
15 N-Ac-Sar-Gly-Val-D-Leu-1Nal-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Leu-Octylgly-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Leu-Gln-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Leu-Met-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Leu-Ser-Nva-Ile-Arg-ProNHCH₂CH₃,
20 N-Ac-Sar-Gly-Val-D-Leu-Allylgly-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Leu-Ile-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Leu-D-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Ile-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nle-Ile-Arg-ProNHCH₂CH₃,
25 N-Ac-Sar-Gly-Val-D-Ile-Thr-Cit-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Met(O₂)-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Arg-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Tyr-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Glu-Ile-Arg-ProNHCH₂CH₃,
30 N-Ac-Sar-Gly-Val-D-Ile-Thr-Lys(Ac)-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Propargylgly-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Leu-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Bala-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
35 N-Phenylacetyl-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Pro-Azagly-NH₂,

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Sar-NHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Pro-SerNH₂,
N-Succinyl-Sar-Gly-Val-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Ala-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
5 N-Ac-Sar-Leu-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Phe-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Glu-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Pro-Val-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
10 N-Ac-Sar-Asn-Val-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Asp-Val-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Asn-Gly-Val-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Gln-Gly-Val-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Ser-Gly-Val-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
15 N-Ac-Cit-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Glu-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Gaba-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Bala-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Gln-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
20 N-Ac-Sar-Gly-Gly-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Glu-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNHCH(CH₃)₂,
N-Succinyl-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
N-Succinyl-Sar-Gly-Val-D-Leu-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
25 N-Succinyl-Sar-Gly-Val-D-Leu-Thr-Gln-Ile-Arg-ProNHCH(CH₃)₂,
N-Ac-Sar-Gly-Val-D-Leu-Thr-Asp-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Asp-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Asn-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Met(O)-Ile-Arg-ProNHCH₂CH₃,
30 N-Ac-Sar-Gly-Val-D-Leu-Thr-Asn-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Thr-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ser-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Hser-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Gln-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Asn-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
35 N-Ac-Sar-Gly-Val-D-Cit-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Hcit-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,

N-Ac-Sar-Gly-Val-D-Hle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Neopentylgly-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Phe(4-COH₂)-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-His-ProNHCH₂CH₃,
5 N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Lys(Isp)-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Lys(Nic)-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Orn(Nic)-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Orn(Isp)-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Phe(4-NIsp)-ProNHCH₂CH₃,
10 N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Cha(4-NIsp)-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Harg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Norarg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Cit-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Lys-ProNHCH₂CH₃,
15 N-Ac-Sar-Gly-Val-D-Ile-Phe(4-CH₂OH)-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Phe(4-guanidino)-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Aminopyrimidinylbutanoyl-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Phe(4-CH₂NHisp)-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Gly[4-Pip(N-amidino)]-ProNHCH₂CH₃,
20 N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Ala[4-Pip(N-amidino)]-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Ala-(3-guanidino)-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Ala(3-pyrrolidinylamidino)-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Orn(2-imidazo)-ProNHCH₂CH₃,
N-Succinyl-Sar-Gly-Val-D-alloIle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
25 N-Succinyl-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
N-Succinyl-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-Pro-D-AlaNH₂,
N-Succinyl-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
N-Succinyl-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-Pro-D-AlaNH₂,
N-Succinyl-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH(CH₃)₂,
30 N-Succinyl-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNHCH(CH₃)₂,
N-Ac-Sar-Gly-Val-D-alloIle-Thr-Nva-Ile-Arg-Pro-D-AlaNH₂,
N-Ac-Sar-Gly-Val-D-alloIle-Thr-Nva-Ile-Arg-ProNHCH(CH₃)₂,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-Pro-D-AlaNH₂,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNHCH(CH₃)₂,
35 N-Ac-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-Pro-D-AlaNH₂,
N-Ac-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH(CH₃)₂,

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Pro-SarNH₂,
N-Ac-Sar-Gly-Val-D-alloIle-Thr-Nva-Ile-Arg-Pro-SarNH₂,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-Pro-SarNH₂,
N-Ac-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-Pro-SarNH₂,
5 N-Ac-Sar-Gly-Val-D-alloIle-Thr-Ser-Ile-Arg-Pro-D-AlaNH₂,
N-Ac-Sar-Gly-Val-D-alloIle-Thr-Ser-Ile-Arg-ProNHCH(CH₃)₂,
N-Ac-Sar-Gly-Val-D-alloIle-Thr-Ser-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Orn(Ac)-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-Pro-AzaglyNH₂,
10 N-Ac-Sar-Gly-Val-D-alloIle-Thr-Nva-Ile-Arg-Pro-AzaglyNH₂,
N-Ac-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-Pro-AzaglyNH₂,
N-(2-THFcarbonyl)-Sar-Gly-Val-D-alloIle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-(2-THFcarbonyl)-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
N-(2-THFcarbonyl)-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
15 N-(2-THFcarbonyl)-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-Pro-D-AlaNH₂,
N-(2-THFcarbonyl)-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-Pro-D-AlaNH₂,
N-(2-THFcarbonyl)-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH(CH₃)₂,
N-(6-Ac-Aca)-Sar-Gly-Val-D-alloIle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-(6-Ac-Aca)-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
20 N-(6-Ac-Aca)-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
N-(6-Ac-Aca)-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-Pro-D-AlaNH₂,
N-(6-Ac-Aca)-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-Pro-D-AlaNH₂,
N-(6-Ac-Aca)-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH(CH₃)₂,
N-(4-Ac-Gaba)-Sar-Gly-Val-D-alloIle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
25 N-(4-Ac-Gaba)-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
N-(4-Ac-Gaba)-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
N-(4-Ac-Gaba)-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-Pro-D-AlaNH₂,
N-(4-Ac-Gaba)-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-Pro-D-AlaNH₂,
N-(4-Ac-Gaba)-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH(CH₃)₂,
30 N-(2-Furoyl)-Sar-Gly-Val-D-alloIle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-(2-Furoyl)-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
N-(2-Furoyl)-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
N-(2-Furoyl)-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-Pro-D-AlaNH₂,
N-(2-Furoyl)-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-Pro-D-AlaNH₂,
35 N-(2-Furoyl)-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH(CH₃)₂,
N-(Shikimyl)-Sar-Gly-Val-D-alloIle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,

N-(Shikimyl)-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
 N-(Shikimyl)-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
 N-(Shikimyl)-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-Pro-D-AlaNH₂,
 N-(Shikimyl)-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-Pro-D-AlaNH₂,
 N-(Shikimyl)-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH(CH₃)₂,
 N-(2-Me-Nicotinyl)-Sar-Gly-Val-D-alloIle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
 N-(2-Me-Nicotinyl)-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
 N-(2-Me-Nicotinyl)-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
 N-(2-Me-Nicotinyl)-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-Pro-D-AlaNH₂,
 N-(2-Me-Nicotinyl)-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-Pro-D-AlaNH₂,
 N-(2-Me-Nicotinyl)-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH(CH₃)₂,
 N-Ac-Sar-Gly-Val-D-alloIle-Thr-Leu-Ile-Arg-Pro-D-AlaNH₂,
 N-Ac-Sar-Gly-Val-D-Ile-Thr-Leu-Ile-Arg-ProNHCH(CH₃)₂,
 N-Ac-Sar-Gly-Val-D-alloIle-Thr-Leu-Ile-Arg-ProNHCH₂CH₃,
 N-Ac-Sar-Gly-Val-D-Ile-Thr-Leu-Ile-Arg-Pro-D-AlaNH₂,
 N-Succinyl-Sar-Gly-Val-D-Ile-Thr-Leu-Ile-Arg-Pro-D-AlaNH₂,
 N-Succinyl-Sar-Gly-Val-D-Ile-Thr-Leu-Ile-Arg-ProNHCH(CH₃)₂,
 N-Succinyl-Sar-Gly-Val-D-Ile-Thr-Leu-Ile-Arg-ProNHCH₂CH₃,
 N-Succinyl-Sar-Gly-Val-D-alloIle-Thr-Leu-Ile-Arg-ProNHCH₂CH₃,
 N-Succinyl-Sar-Gly-Val-D-alloIle-Thr-Leu-Ile-Arg-Pro-D-AlaNH₂,
 N-Succinyl-Sar-Gly-Val-D-Ile-Thr-Leu-Ile-Arg-Pro-AzaglyNH₂,
 N-Ac-Sar-Gly-Val-D-alloIle-Thr-Nva-Ile-Arg-ProNHethyl-(1-pyrrolidine),
 N-Ac-Sar-Gly-Val-D-alloIle-Thr-Nva-Ile-Arg-ProNH(ethyl-1-cyclohexyl),
 N-Ac-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNHethyl-(1-pyrrolidine),
 N-Ac-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNH(ethyl-1-cyclohexyl),
 N-Succinyl-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNH(ethyl-1-cyclohexyl),
 N-Ac-Sar-Gly-Val-D-alloIle-Thr-Nva-Ile-Arg-ProNHCH₂CH₂OCH₃,
 N-Ac-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNHCH₂CH₂OCH₃,
 N-Ac-Sar-Gly-Val-D-Ile-Thr-Ser-Ile-Arg-ProNHCH₂CH₂OCH₃,
 N-Ac-Sar-Gly-Val-D-Ile-Thr-Leu-Ile-Arg-ProNHCH₂CH₂OCH₃,
 N-Succinyl-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₂OCH₃,
 N-Succinyl-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNHCH₂CH₂OCH₃,
 N-Succinyl-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH₂CH₂OCH₃,
 N-Ac-Sar-Gly-Val-D-Ile-Ser-Nva-Ile-Arg-ProNHCH₂CH₂OCH₃,
 N-Ac-Sar-Gly-Val-D-Leu-Ser-Nva-Ile-Arg-ProNHCH₂CH₂OCH₃,
 N-Ac-Sar-Gly-Val-D-alloIle-Thr-Allygly-Ile-Arg-ProNHCH₂CH₃,

N-Ac-Sar-Gly-Val-D-Ile-Thr-Allygly-Ile-Arg-ProNHCH(CH₃)₂,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Allygly-Ile-Arg-Pro-D-AlaNH₂,
N-Ac-Sar-Gly-Val-D-alloIle-Thr-Allygly-Ile-Arg-Pro-D-AlaNH₂,
N-Succinyl-Sar-Gly-Val-D-Ile-Thr-Allygly-Ile-Arg-Pro-D-AlaNH₂,
5 N-Ac-Sar-Gly-Val-D-Ile-Ser-Allygly-Ile-Arg-Pro-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Leu-Ser-Allygly-Ile-Arg-Pro-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Pro-SarNH₂,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHOH,
N-Ac-Sar-Gly-Val-D-Ile-Ser-Nva-Ile-Arg-ProNHCH₂CH₃,
10 N-Ac-Sar-Gly-Val-D-alloIle-Ser-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Leu-Hser-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Gln-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Nva-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
15 N-Ac-Sar-Gly-Ile-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Phe-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Leu-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Ser-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Thr-Gly-Val-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-alloIle-Thr-Ala-Ile-Arg-ProNHCH₂CH₃,
20 N-Ac-Sar-Gly-Val-D-Ile-Thr-Ala-Ile-Arg-ProNHCH(CH₃)₂,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Ala-Ile-Arg-Pro-D-AlaNH₂,
N-Ac-Sar-Gly-Val-D-alloIle-Thr-Ala-Ile-Arg-Pro-D-AlaNH₂,
N-Succinyl-Sar-Gly-Val-D-Ile-Thr-Ala-Ile-Arg-Pro-D-AlaNH₂,
N-Ac-Sar-Gly-Val-D-Ile-Ser-Ala-Ile-Arg-ProNHCH₂CH₃,
25 N-Ac-Sar-Gly-Val-D-Leu-Ser-Ala-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-alloIle-Thr-Val-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Val-Ile-Arg-ProNHCH(CH₃)₂,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Val-Ile-Arg-Pro-D-AlaNH₂,
N-Ac-Sar-Gly-Val-D-alloIle-Thr-Val-Ile-Arg-Pro-D-AlaNH₂,
30 N-Succinyl-Sar-Gly-Val-D-Ile-Thr-Val-Ile-Arg-Pro-D-AlaNH₂,
N-Ac-Sar-Gly-Val-D-Ile-Ser-Val-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Leu-Ser-Val-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-alloIle-Thr-D-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-D-Nva-Ile-Arg-ProNHCH(CH₃)₂,
35 N-Ac-Sar-Gly-Val-D-Ile-Thr-D-Nva-Ile-Arg-Pro-D-AlaNH₂,
N-Ac-Sar-Gly-Val-D-alloIle-Thr-D-Nva-Ile-Arg-Pro-D-AlaNH₂,

N-Succinyl-Sar-Gly-Val-D-Ile-Thr-D-Nva-Ile-Arg-Pro-D-AlaNH₂,
N-Ac-Sar-Gly-Val-D-Ile-Ser-D-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Leu-Ser-D-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Ser-Gln-Ile-Arg-ProNHCH₂CH₃,
5 N-Ac-Sar-Gly-Val-D-Leu-Ser-Gln-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Leu-Ser-Nva-Ile-Arg-Pro-D-AlaNH₂,
N-Ac-Sar-Gly-Val-D-Ile-Ser-Nva-Ile-Arg-Pro-D-AlaNH₂,
N-Succinyl-Sar-Gly-Val-D-Leu-Ser-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Succinyl-Sar-Gly-Val-D-Ile-Ser-Nva-Ile-Arg-ProNHCH₂CH₃,
10 N-Succinyl-Sar-Gly-Val-D-Leu-Ser-Gln-Ile-Arg-ProNHCH₂CH₃,
N-Succinyl-Sar-Gly-Val-D-Ile-Ser-Gln-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Ser-Ser-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Leu-Ser-Ser-Ile-Arg-ProNHCH₂CH₃,
15 N-Ac-Sar-Gly-Val-D-Leu-Ser-Nva-Ile-Arg-ProNHCH(CH₃)₂,
N-Ac-Sar-Gly-Val-D-Ile-Ser-Nva-Ile-Arg-ProNHCH(CH₃)₂,
N-Ac-Sar-Gly-Val-D-Leu-Ser-Leu-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Ser-Leu-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-alloIle-Ser-Nva-Ile-Arg-ProNHCH₂CH₃,
20 N-Succinyl-Sar-Gly-Val-D-alloIle-Ser-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-alloIle-Ser-Nva-Ile-Arg-ProNHCH(CH₃)₂,
N-Ac-Sar-Gly-Val-D-alloIle-Ser-Nva-Ile-Arg-Pro-D-AlaNH₂,
N-Ac-Sar-Gly-Val-D-alloIle-Ser-Leu-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-alloIle-Ser-Ser-Ile-Arg-ProNHCH₂CH₃,
25 N-Ac-Sar-Gly-Val-D-Ile-Gly-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-alloIle-Gly-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Leu-Gly-Gln-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Gly-Gln-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-alloIle-Gly-Gln-Ile-Arg-ProNHCH₂CH₃,
30 N-Ac-Sar-Gly-Val-D-Ile-Tyr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-alloIle-Tyr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Leu-Tyr-Gln-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Tyr-Gln-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-alloIle-Tyr-Gln-Ile-Arg-ProNHCH₂CH₃,
35 N-Ac-Sar-Gly-Val-D-Ser-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Thr-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,

N-Ac-Sar-Gly-Val-D-Gln-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Asn-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Arg-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-3-Pal-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
5 N-Ac-Sar-Gly-Val-D-Glu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Asp-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-His-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Hser-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-alloThr-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
10 N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-D-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ser-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Thr-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-alloThr-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ser-Ser-Nva-Ile-Arg-ProNHCH₂CH₃,
15 N-Ac-Sar-Gly-Val-D-Thr-Ser-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-alloThr-Ser-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-alloThr-Ser-Gln-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Thr-Ser-Gln-Ile-Arg-ProNHCH₂CH₃,
N-(6-Ac-Aca)-Sar-Gly-Val-D-Leu-Ser-Gln-Ile-Arg-ProNHCH(CH₃)₂,
20 N-(6-Ac-Aca)-Sar-Gly-Val-D-Leu-Ser-Nva-Ile-Arg-ProNHCH(CH₃)₂,
N-(4-Ac-Gaba)-Sar-Gly-Val-D-Leu-Ser-Gln-Ile-Arg-ProNHCH(CH₃)₂,
N-(4-Ac-Gaba)-Sar-Gly-Val-D-Leu-Ser-Nva-Ile-Arg-ProNHCH(CH₃)₂,
N-(2-Furoyl)-Sar-Gly-Val-D-Leu-Ser-Gln-Ile-Arg-ProNHCH(CH₃)₂,
N-(2-Furoyl)-Sar-Gly-Val-D-Leu-Ser-Nva-Ile-Arg-ProNHCH(CH₃)₂,
25 N-(Shikimyl)-Sar-Gly-Val-D-Leu-Ser-Gln-Ile-Arg-ProNHCH(CH₃)₂,
N-(Shikimyl)-Sar-Gly-Val-D-Leu-Ser-Nva-Ile-Arg-ProNHCH(CH₃)₂,
N-(Shikimyl)-Sar-Gly-Val-D-Leu-Ser-Gln-Ile-Arg-ProNHCH(CH₃)₂,
N-(Shikimyl)-Sar-Gly-Val-D-Leu-Ser-Nva-Ile-Arg-ProNHCH(CH₃)₂,
N-(2-Me-nicotinyl)-Sar-Gly-Val-D-Leu-Ser-Gln-Ile-Arg-ProNHCH(CH₃)₂,
30 N-(2-Me-nicotinyl)-Sar-Gly-Val-D-Leu-Ser-Nva-Ile-Arg-ProNHCH(CH₃)₂,
N-Ac-Sar-Gly-Val-D-Leu-Ser-Nva-Ile-Arg-ProNHethyl-1-(R)-cyclohexyl,
N-Ac-Sar-Gly-Val-D-Leu-Ser-Gln-Ile-Arg-ProNHethyl-1-(R)-cyclohexyl,
N-Ac-Sar-Gly-Val-DIle-Thr-Ser-Ile-Arg-ProNHethyl-1-(R)-cyclohexyl,
N-Ac-Sar-Gly-Val-D-Leu-Thr-Nva-Ile-Arg-ProNHethyl-1-(R)-cyclohexyl,
35 N-Ac-Sar-Gly-Val-D-Leu-Ser-Ser-Ile-Arg-ProNHethyl-1-(R)-cyclohexyl,
N-Ac-Sar-Gly-Val-DIle-Thr-Nva-Ile-Arg-ProNHethyl-1-(S)-cyclohexyl,

N-Ac-Sar-Gly-Val-D-Pen-Ser-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Pen-Gly-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Pen-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Pen-Ser-Nva-Ile-Arg-ProNHCH(CH₃)₂,
5 N-Succinyl-Sar-Gly-Val-D-Pen-Ser-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Pen-Ser-Nva-Ile-Arg-Pro-D-AlaNH₂,
N-Ac-Sar-Gly-Val-D-Pen-Ser-Gln-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Pen-Gly-Gln-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Pen-Ser-Ser-Ile-Arg-ProNHCH₂CH₃,
10 N-Ac-Sar-Gly-Val-D-Pen-Thr-Ser-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Pen-Thr-Leu-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Pen-Ser-Leu-Ile-Arg-ProNHCH₂CH₃,
N-Succinyl-Sar-Gly-Val-D-Pen-Ser-Ser-Ile-Arg-ProNHCH₂CH₃,
N-Succinyl-Sar-Gly-Val-D-Pen-Ser-Leu-Ile-Arg-ProNHCH₂CH₃,
15 N-Succinyl-Sar-Gly-Val-D-Pen-Thr-Gln-Ile-Arg-ProNHCH(CH₃)₂,
N-Ac-Sar-Gly-Val-D-Cys-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Cys-Ser-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Cys-Gly-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Cys-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
20 N-Ac-Sar-Gly-Val-D-Cys-Ser-Nva-Ile-Arg-ProNHCH(CH₃)₂,
N-Succinyl-Sar-Gly-Val-D-Cys-Ser-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Cys-Ser-Nva-Ile-Arg-Pro-D-AlaNH₂,
N-Ac-Sar-Gly-Val-D-Cys-Ser-Gln-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Cys-Gly-Gln-Ile-Arg-ProNHCH₂CH₃,
25 N-Ac-Sar-Gly-Val-D-Cys-Ser-Ser-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Cys-Thr-Ser-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Cys-Thr-Leu-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Cys-Ser-Leu-Ile-Arg-ProNHCH₂CH₃,
N-Succinyl-Sar-Gly-Val-D-Cys-Ser-Ser-Ile-Arg-ProNHCH₂CH₃,
30 N-Succinyl-Sar-Gly-Val-D-Cys-Ser-Leu-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Pen-DIle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Cys-DIle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Pen-D-alloIle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Pen-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
35 N-Ac-Sar-Gly-Pen-D-Ile-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Pen-D-Ile-Ser-Nva-Ile-Arg-ProNHCH₂CH₃,

N-Ac-Sar-Gly-Pen-D-Ile-Thr-Nva-Ile-Arg-ProNHCH(CH₃)₂,
N-Ac-Sar-Gly-Pen-D-Ile-Thr-Nva-Ile-Arg-Pro-D-AlaNH₂,
N-Succinyl-Gly-Pen-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Succinyl-Sar-Gly-Pen-D-Ile-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
5 N-Succinyl-Sar-Gly-Pen-D-Ile-Thr-Gln-Ile-Arg-ProNHCH(CH₃)₂,
N-Ac-Sar-Gly-Val-D-Leu-Pen-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Pen-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-alloIle-Pen-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Pen-Gln-Ile-Arg-ProNHCH₂CH₃,
10 N-Ac-Sar-Gly-Val-D-Ile-Pen-Ser-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Pen-Leu-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Pen-Nva-Ile-Arg-ProNHCH(CH₃)₂,
N-Ac-Sar-Gly-Val-D-Ile-Pen-Nva-Ile-Arg-Pro-D-AlaNH₂,
N-Succinyl-Sar-Gly-Val-D-Ile-Pen-Nva-Ile-Arg-ProNHCH₂CH₃,
15 N-Succinyl-Sar-Gly-Val-D-Ile-Pen-Gln-Ile-Arg-ProNHCH₂CH₃,
N-Succinyl-Sar-Gly-Val-D-Ile-Pen-Gln-Ile-Arg-ProNHCH(CH₃)₂,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Pen-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-alloIle-Thr-Pen-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Leu-Thr-Pen-Ile-Arg-ProNHCH₂CH₃,
20 N-Ac-Sar-Gly-Val-D-Ile-Thr-Pen-Ile-Arg-Pro-D-AlaNH₂,
N-Succinyl-Sar-Gly-Val-D-Ile-Thr-Pen-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Pen-Ile-Arg-ProNHCH(CH₃)₂,
N-Ac-Sar-Gly-Val-D-Leu-Ser-Pen-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Leu-Gly-Pen-Ile-Arg-ProNHCH₂CH₃,
25 N-Succinyl-Sar-Gly-Val-D-Leu-Ser-Pen-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Phe(3,4,5-triF)-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Phe(3,4,5-triF)-Ser-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Phe(3,4,5-triF)-Gly-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Phe(3,4,5-triF)-Ser-Leu-Ile-Arg-ProNHCH₂CH₃,
30 N-Ac-Sar-Gly-Val-D-Phe(3,4,5-triF)-Ser-Nva-Ile-Arg-Pro-D-AlaNH₂,
N-Succinyl-Sar-Gly-Val-D-Phe(3,4,5-triF)-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
N-Succinyl-Sar-Gly-Val-D-Phe(3,4,5-triF)-Ser-Gln-Ile-Arg-ProNHCH₂CH₃,
N-Succinyl-Sar-Gly-Val-D-Phe(3,4,5-triF)-Thr-Gln-Ile-Arg-ProNHCH(CH₃)₂,
N-Ac-Sar-Gly-Val-D-Phe(3,4,5-triF)-Ser-Gln-Ile-Arg-ProNHCH₂CH₃,
35 N-Ac-Sar-Gly-Val-D-Phe(3,4,5-triF)-Ser-Ser-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Ala-Val-D-alloIle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,

N-Ac-Sar-Ala-Val-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Ala-Val-D-Ile-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Ala-Val-D-Leu-Ser-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Ala-Val-D-Leu-Ser-Gln-Ile-Arg-ProNHCH₂CH₃,
5 N-Succinyl-Sar-Ala-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Succinyl-Sar-Ala-Val-D-Ile-Thr-Gln-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Succinyl-Sar-Ala-Val-D-Ile-Thr-Gln-Nva-Ile-Arg-ProNHCH(CH₃)₂,
N-Succinyl-Sar-Ala-Val-D-Ile-Thr-Gln-Nva-Ile-Arg-Pro-D-AlaNH₂,
N-(3-Ac-Bala)-Sar-Gly-Val-D-alloIle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
10 N-(3-Ac-Bala)-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
N-(3-Ac-Bala)-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
N-(3-Ac-Bala)-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-Pro-D-AlaNH₂,
N-(3-Ac-Bala)-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-Pro-D-AlaNH₂,
N-(3-Ac-Bala)-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH(CH₃)₂,
15 N-(3-Ac-Bala)-Sar-Gly-Val-D-Leu-Ser-Nva-Ile-Arg-ProNHCH₂CH₃,
N-(3-Ac-Bala)-Sar-Gly-Val-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-(3-Ac-Bala)-Sar-Gly-Val-D-Pen-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-(3-Ac-Bala)-Sar-Gly-Val-D-Ile-Ser-Nva-Ile-Arg-ProNHCH₂CH₃,
N-(3-Ac-Bala)-Sar-Ala-Val-D-alloIle-Ser-Nva-Ile-Arg-ProNHCH₂CH₃,
20 N-(3-Ac-Bala)-Sar-Ala-Val-D-Ile-Ser-Nva-Ile-Arg-ProNHCH₂CH₃,
N-(3-Ac-Bala)-Sar-Ala-Val-D-Leu-Ser-Nva-Ile-Arg-ProNHCH₂CH₃,
N-(3-Ac-Bala)-Sar-Ala-Val-D-Leu-Ser-Gln-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Pro-OH,
N-Ac-Sar-Gly-Val-D-alloIle-Thr-Nva-Ile-Arg-Pro-OH,
25 N-Ac-Sar-Gly-Val-D-Leu-Thr-Nva-Ile-Arg-Pro-OH,
N-Ac-Sar-Gly-Val-D-Pen-Thr-Nva-Ile-Arg-Pro-OH,
N-Ac-Sar-Gly-Val-D-Phe(3,4,5-triF)-Thr-Nva-Ile-Arg-Pro-OH,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-Pro-OH,
N-Ac-Sar-Gly-Val-D-Leu-Ser-Nva-Ile-Arg-Pro-OH,
30 N-Ac-Sar-Ala-Val-D-Ile-Thr-Nva-Ile-Arg-Pro-OH,
N-Ac-Sar-Gly-Val-D-Ile-Ser-Gln-Ile-Arg-Pro-OH,
N-Succinyl-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Pro-OH,
N-Succinyl-Sar-Gly-Val-D-Leu-Thr-Gln-Ile-Arg-Pro-OH
N-Ac-Sar-Gly-Asp-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
35 N-Ac-Sar-Gly-Ala-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Cha-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,

N-Ac-Sar-Gly-Met-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Hser-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Cit-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-alloIle-His-Nva-Ile-Arg-ProNHCH₂CH₃,
5 N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNH-n-Butyl,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNH-iso-Butyl,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNH-iso-Amyl,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNH-n-hexyl,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNH-(3,3-dimethyl)butyl,
10 N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNH-(2-ethoxy)ethyl,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNH-(2-isopropoxy)ethyl,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNH-(3-methoxy)propyl,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNH-(cyclopentyl)methyl,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNH-cyclohexyl,
15 N-Ac-Sar-Gly-Gln-DIle-Thr-Nva-Ile-Arg-Pro-DAlaNH₂,
N-Ac-Sar-Gly-Phe-DIle-Thr-Nva-Ile-Arg-Pro-DAlaNH₂,
N-Ac-Sar-Gln-Val-DIle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-DIle-alloThr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-DIle-Thr-Nva-DIle-Arg-ProNHCH₂CH₃,
20 N-Ac-Sar-Gly-Asn-DLeu-Ser-Nva-Ile-Arg-ProNHCH₂CH₃,
N-(6-Me-Nicotinyl)-Sar-Gly-Val-DIle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-Ile-Thr-Nva-DIle-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-DalloIle-Ser-Thr-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Gln-DIle-Thr-Nva-DIle-Arg-ProNHCH₂CH₃,
25 N-Ac-Sar-Gly-Asn-DIle-Thr-Nva-Lys(Ac)-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Gln-DalloIle-Tyr-Nva-DIle-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Gln-DalloIle-Thr-Nva-Ile-Arg-Pro-DAlaNH₂,
N-Ac-Sar-Gly-Asn-DLeu-Thr-Ser-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-DIle-alloThr-Ser-Ile-Arg-ProNHCH₂CH₃,
30 N-Ac-Sar-Gly-Gln-DIle-alloThr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-DIle-alloThr-Nva-Pro-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-DalloIle-Thr-Trp-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-DalloIle-Ser-Ser-Ile-Arg-ProNHCH(CH₃)₂,
N-Ac-Sar-Gly-Val-DIle-Thr-Gln-DIle-Arg-ProNHCH₂CH₃,
35 N-Ac-Sar-Gly-Val-DalloIle-Thr-Trp-DIle-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-DalloIle-Thr-Nva-Ile-Arg-DProNHCH₂CH₃,

N-Ac-Sar-Gly-Val-DIle-Met-Nva-Ile-Arg-Pro-DAlaNH₂,
N-Ac-Sar-Gly-Val-DIle-alloThr-Pro-Arg-Pro-NHCH₂CH₃,
N-Ac-Sar-Gly-Val-DalloIle-alloThr-Gln-Ile-Arg-ProNHCH₂CH₃, and
N-Ac-Sar-Gly-Val-DalloIle-Ser-Ser-Ile-Arg-Pro-DAlaNH₂.

5

Preferred compounds for the practice of the invention are:

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₂-(1-pyrrolidine),
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNH(ethyl-1-(R)-cyclohexyl),
10 N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNH₂,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH(CH₃)₂,
N-Ac-Sar-Gly-Val-D-alloIle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Val-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
15 N-Ac-Sar-Gly-Val-D-Nle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Phe-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Cha-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-3,4-diClPhe-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-3-ClPhe-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
20 N-Ac-Sar-Gly-Val-D-2-Thienylala-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-3-CNPhe-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Cha-Ile-Arg-ProNHCH₂CH₃,
N[2-THFcarbonyl]-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
25 N[6-N-acetyl-(CH₂)₅C(O)]-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Hexanoyl-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-[4-N-Acetylaminobutyryl]-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
30 N-[CH₃C(O)NH-(CH₂)₂-O-(CH₂)₂-O-CH₂-C(O)]-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-
ProNHCH₂CH₃,
N-Ac-Pro-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-NEtGly-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
35 N-Ac-Sar-Gly-Val-D-Ile-Thr-Leu-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Ser-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Pro-D-AlaNH₂,
N-Ac-Sar-Gly-Val-D-Leu-Thr-Nva-Lys(Ac)-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Leu-Thr-Nva-Leu-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Leu-Thr-Nva-1Nal-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Leu-Thr-Nva-Allylgly-Arg-ProNHCH₂CH₃,

(continued)

N-Ac-Sar-Gly-Val-D-Leu-Ala-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Leu-Trp-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Leu-Tyr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Leu-Gly-Nva-Ile-Arg-ProNHCH₂CH₃,
5 N-Ac-Sar-Gly-Val-D-Leu-2Nal-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Leu-1Nal-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Leu-Octylgly-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Leu-Ser-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Leu-Allylgly-Nva-Ile-Arg-ProNHCH₂CH₃,
10 N-Ac-Sar-Gly-Val-D-Leu-D-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Tyr-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Glu-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Propargylgly-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
15 N-Ac-Bala-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Phenylacetyl-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Pro-AzaglyNH₂,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Pro-SerNH₂,
N-(6-Ac-Aca)-Sar-Gly-Val-D-Leu-Ser-Gln-Ile-Arg-ProNHCH(CH₃)₂,
20 N-(6-Ac-Aca)-Sar-Gly-Val-D-Leu-Ser-Nva-Ile-Arg-ProNHCH(CH₃)₂,
N-(4-Ac-Gaba)-Sar-Gly-Val-D-Leu-Ser-Gln-Ile-Arg-ProNHCH(CH₃)₂,
N-(4-Ac-Gaba)-Sar-Gly-Val-D-Leu-Ser-Nva-Ile-Arg-ProNHCH(CH₃)₂,
N-(2-Furoyl)-Sar-Gly-Val-D-Leu-Ser-Gln-Ile-Arg-ProNHCH(CH₃)₂,
N-(2-Furoyl)-Sar-Gly-Val-D-Leu-Ser-Nva-Ile-Arg-ProNHCH(CH₃)₂,
25 N-(Shikimyl)-Sar-Gly-Val-D-Leu-Ser-Gln-Ile-Arg-ProNHCH(CH₃)₂,
N-(Shikimyl)-Sar-Gly-Val-D-Leu-Ser-Nva-Ile-Arg-ProNHCH(CH₃)₂,
N-(Shikimyl)-Sar-Gly-Val-D-Leu-Ser-Gln-Ile-Arg-ProNHCH(CH₃)₂,
N-(Shikimyl)-Sar-Gly-Val-D-Leu-Ser-Nva-Ile-Arg-ProNHCH(CH₃)₂,
N-(2-Me-nicotinyl)-Sar-Gly-Val-D-Leu-Ser-Gln-Ile-Arg-ProNHCH(CH₃)₂,
30 N-(2-Me-nicotinyl)-Sar-Gly-Val-D-Leu-Ser-Nva-Ile-Arg-ProNHCH(CH₃)₂,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Pro-OH,
N-Ac-Sar-Ala-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Pen-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Phe(3,4,5-triF)-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
35 N-Ac-Sar-Gly-Val-D-Phe(4-NH₂)-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-alloIle-Ser-Gln-Ile-Arg-ProNHCH₂CH₃,

N-Ac-Sar-Gly-Val-D-alloIle-Ser-Ser-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Gln-D-Ile-Thr-Nva-Ile-Arg-Pro-DAlaNH₂,
N-Ac-Sar-Gly-Val-D-Ile-alloThr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Gln-D-Ile-Thr-Nva-DIle-Arg-ProNHCH₂CH₃, and
5 N-Ac-Sar-Gly-Gln-D-alloIle-Tyr-Nva-DIle-Arg-ProNHCH₂CH₃.

It is well known in the art that modifications and changes can be made in the structure of a polypeptide without substantially altering the biological function of that peptide. For example, certain amino acids can be substituted for other amino acids in a 10 given polypeptide without any appreciable loss of function. In making such changes, substitutions of like amino acid residues can be made on the basis of relative similarity of side-chain substituents, for example, their size, charge, hydrophobicity, hydrophilicity, and the like. In describing the invention, certain abbreviations are used for the sake of convenience throughout the specification, including the examples, to refer to reagents and 15 compounds useful for preparing the compounds of the invention. When so used, the following abbreviations are meant to refer to the following: DMF for dimethylformamide; DMA for dimethylacetamide; DIEA for diisopropylethylamine; HATU for O-(7-aza-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate; NMP for N-methylpyrrolidone; and TFA for trifluoroacetic acid.

20 **Determination of Biological Activity**
Pellet Preparation

Ten microliters of a mixture containing a final concentration of 1, 5, or 10 mM of the peptides of invention, 100 ng of bFGF (Collaborative Biomedical Products, Bedford, 25 MA), and 6% Hydron (Sigma, St. Louis, MO) were pipetted into the tip of a sterile Teflon rod. After drying for 1-2 hours, the pellets were stored at 4 °C.

Pellet Implantation

A small (about 2 mm) radial incision at 1 mm from the center of the cornea was 30 performed in anesthetized Sprague Dawley rats. With a curved iris spatula, an intrastromal pocket was made to a distance of 1 mm from the limbus-the circular blood vessels that surround the cornea. A single pellet was implanted. Antibiotic ointment (neosporin) was applied post surgery to the operated eye to prevent infection and to decrease inflammation.

35 **Data Analysis**

At day seven post-implantation, neovascularization was measured through a slitlamp biomicroscopy (Nikon NS-1), connected to an image analysis system (Leica Qwin). The response was calculated by colorimetrically detecting the area of new blood vessels, and calculating the new vessel surface area in μm^2 . The compounds of the invention inhibit rat cornea neovascularization as shown in Table 2.

Table 2
Effect of the Compounds of the Invention on Rat Cornea Neovascularization

Peptide	Number of Corneas/Dose	% Inhibition
Example 1	6/10 μM	92.6
Example 1	5/5 μM	74.8
Example 1	4/6 μM	71.5
untreated	5/-	-

The compounds of the invention, including but not limited to those specified in the examples, possess anti-angiogenic activity. As angiogenesis inhibitors, such compounds are useful in the treatment of both primary and metastatic solid tumors, including carcinomas of breast, colon, rectum, lung, oropharynx, hypopharynx, esophagus, stomach, pancreas, liver, gallbladder and bile ducts, small intestine, urinary tract (including kidney, bladder and urothelium), female genital tract, (including cervix, uterus, and ovaries as well as choriocarcinoma and gestational trophoblastic disease), male genital tract (including prostate, seminal vesicles, testes and and germ cell tumors), endocrine glands (including the thyroid, adrenal, and pituitary glands), and skin, as well as hemangiomas, melanomas, sarcomas (including those arising from bone and soft tissues as well as Kaposi's sarcoma) and tumors of the brain, nerves, eyes, and meninges (including astrocytomas, gliomas, glioblastomas, retinoblastomas, neuromas, neuroblastomas, Schwannomas, and meningiomas). Such compounds may also be useful in treating solid tumors arising from hematopoietic malignancies such as leukemias (i.e. chloromas, plasmacytomas and the plaques and tumors of mycosis fungoides and cutaneous T-cell lymphoma/leukemia) as well as in the treatment of lymphomas (both Hodgkin's and non-Hodgkin's lymphomas). In addition, these compounds may be useful in the prevention of metastases from the tumors described above either when used alone or in combination with radiotherapy and/or other chemotherapeutic agents.

Further uses include the treatment and prophylaxis of autoimmune diseases such as rheumatoid, immune and degenerative arthritis; various ocular diseases such as diabetic retinopathy, retinopathy of prematurity, corneal graft rejection, retrobulbar fibroplasia,

neovascular glaucoma, rubeosis, retinal neovascularization due to macular degeneration, hypoxia, angiogenesis in the eye associated with infection or surgical intervention, and other abnormal neovascularization conditions of the eye; skin diseases such as psoriasis; blood vessel diseases such as hemangiomas, and capillary proliferation within

5 atherosclerotic plaques; Osler-Webber Syndrome; myocardial angiogenesis; plaque neovascularization; telangiectasia; hemophiliac joints ; angiofibroma; and wound granulation. Other uses include the treatment of diseases characterized by excessive or abnormal stimulation of endothelial cells, including but not limited to intestinal adhesions, Crohn's disease, atherosclerosis, scleroderma, and hypertrophic scars, i.e. keloids.

10 Another use is as a birth control agent, by inhibiting ovulation and establishment of the placenta. The compounds of the invention are also useful in the treatment of diseases that have angiogenesis as a pathologic consequence such as cat scratch disease (*Rochele minalia quintosa*) and ulcers (*Helicobacter pylori*). The compounds of the invention are also useful to reduce bleeding by administration prior to surgery, especially for the

15 treatment of resectable tumors.

The compounds of the invention may be used in combination with other compositions and procedures for the treatment of diseases. For example, a tumor may be treated conventionally with surgery, radiation or chemotherapy combined with a peptide of the present invention and then a peptide of the present invention may be subsequently administered to the patient to extend the dormancy of micrometastases and to stabilize and inhibit the growth of any residual primary tumor. Additionally, the compounds of the invention may be combined with pharmaceutically acceptable excipients, and optionally sustained-release matrices, such as biodegradable polymers, to form therapeutic compositions.

25 A sustained-release matrix, as used herein, is a matrix made of materials, usually polymers, which are degradable by enzymatic or acid-base hydrolysis or by dissolution. Once inserted into the body, the matrix is acted upon by enzymes and body fluids. A sustained-release matrix desirably is chosen from biocompatible materials such as liposomes, polylactides (polylactic acid), polyglycolide (polymer of glycolic acid),

30 polylactide co-glycolide (copolymers of lactic acid and glycolic acid) polyanhydrides, poly(ortho)esters, polypeptides, hyaluronic acid, collagen, chondroitin sulfate, carboxylic acids, fatty acids, phospholipids, polysaccharides, nucleic acids, polyamino acids, amino acids such as phenylalanine, tyrosine, isoleucine, polynucleotides, polyvinyl propylene, polyvinylpyrrolidone and silicone. A preferred biodegradable matrix is a matrix of one of

35 either polylactide, polyglycolide, or polylactide co-glycolide (co-polymers of lactic acid and glycolic acid).

When used in the above or other treatments, a therapeutically effective amount of one of the compounds of the present invention may be employed in pure form or, where such forms exist, in pharmaceutically acceptable salt form. By a "therapeutically effective amount" of the compound of the invention is meant a sufficient amount of the compound 5 to treat an angiogenic disease, (for example, to limit tumor growth or to slow or block tumor metastasis) at a reasonable benefit/risk ratio applicable to any medical treatment. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any 10 particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of the specific compound employed; the specific composition employed, the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or 15 coincidental with the specific compound employed; and like factors well known in the medical arts. For example, it is well within the skill of the art to start doses of the compound at levels lower than those required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved.

The compounds of the present invention can be used in the form of salts derived 20 from inorganic or organic acids. These salts include but are not limited to the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethansulfonate (isothionate), lactate, maleate, methanesulfonate, nicotinate, 25 2-naphthalenesulfonate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, phosphate, glutamate, bicarbonate, *p*-toluenesulfonate and undecanoate. Water or oil-soluble or dispersible products are thereby obtained.

Examples of acids which may be employed to form pharmaceutically acceptable 30 acid addition salts include such inorganic acids as hydrochloric acid, sulphuric acid and phosphoric acid and such organic acids as acetic acid, maleic acid, succinic acid and citric acid. Other salts include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium or with organic basis. Preferred salts of the compounds of the invention include phosphate, tris and acetate.

35 Alternatively, a compound of the present invention may be administered as pharmaceutical compositions containing the compound of interest in combination with one

or more pharmaceutically acceptable excipients. A pharmaceutically acceptable carrier or excipient refers to a non-toxic solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The compositions may be administered parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, 5 ointments, drops or transdermal patch), rectally, or buccally. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

Pharmaceutical compositions for parenteral injection comprise pharmaceutically-acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, 10 as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), carboxymethylcellulose and suitable mixtures thereof, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate. Proper 15 fluidity may be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservative, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of 20 microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form may be brought about by the 25 inclusion of agents which delay absorption, such as aluminum monostearate and gelatin.

Injectable depot forms are made by forming microencapsule matrices of the drug in 30 biodegradable polymers such as polylactide-polyglycolide, poly(orthoesters), poly(anhydrides), and (poly)glycols, such as PEG. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

The injectable formulations may be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium just prior to use.

Topical administration includes administration to the skin or mucosa, including 35 surfaces of the lung and eye. Compositions for topical administration, including those for

inhalation, may be prepared as a dry powder which may be pressurized or non-pressurized. In non-pressurized powder compositions, the active ingredient in finely divided form may be used in admixture with a larger-sized pharmaceutically-acceptable inert carrier comprising particles having a size, for example, of up to 100 micrometers in diameter.

5 Suitable inert carriers include sugars such as lactose. Desirably, at least 95% by weight of the particles of the active ingredient have an effective particle size in the range of 0.01 to 10 micrometers.

Alternatively, the composition may be pressurized and contain a compressed gas, such as nitrogen or a liquified gas propellant. The liquified propellant medium and indeed 10 the total composition is preferably such that the active ingredient does not dissolve therein to any substantial extent. The pressurized composition may also contain a surface active agent, such as a liquid or solid non-ionic surface active agent or may be a solid anionic surface active agent. It is preferred to use the solid anionic surface active agent in the form of a sodium salt.

15 A further form of topical administration is to the eye. A compound of the invention is delivered in a pharmaceutically acceptable ophthalmic vehicle, such that the compound is maintained in contact with the ocular surface for a sufficient time period to allow the compound to penetrate the corneal and internal regions of the eye, as for example the anterior chamber, posterior chamber, vitreous body, aqueous humor, vitreous 20 humor, cornea, iris/ciliary, lens, choroid/retina and sclera. The pharmaceutically-acceptable ophthalmic vehicle may, for example, be an ointment, vegetable oil or an encapsulating material. Alternatively, the compounds of the invention may be injected directly into the vitreous and aqueous humour.

Compositions for rectal or vaginal administration are preferably suppositories 25 which may be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at room temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Compounds of the present invention may also be administered in the form of 30 liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically-acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present 35 invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and the phosphatidyl cholines (lecithins), both natural and synthetic.

Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 *et seq.*

While the compounds of the invention can be administered as the sole active pharmaceutical agent, they may also be used in combination with one or more agents

- 5 which are conventionally administered to patients for treating angiogenic diseases. For example, the compounds of the invention are effective over the short term to make tumors more sensitive to traditional cytotoxic therapies such as chemicals and radiation. The compounds of the invention also enhance the effectiveness of existing cytotoxic adjuvant anti-cancer therapies. The compounds of the invention may also be combined with other
- 10 antiangiogenic agents to enhance their effectiveness, or combined with other antiangiogenic agents and administered together with other cytotoxic agents. In particular, when used in the treatment of solid tumors, compounds of the invention may be administered with IL-12, retinoids, interferons, angiostatin, endostatin, thalidomide, thrombospondin-1, thrombospondin-2, captopril, angioinhibins, TNP-470, pentosan
- 15 polysulfate, platelet factor 4, LM-609, SU-5416, CM-101, Tecogalan, plasminogen-K-5, vasostatin, vitaxin, vasculostatin, squalamine, marimastat or other MMP inhibitors, anti-neoplastic agents such as alpha interferon, COMP (cyclophosphamide, vincristine, methotrexate and prednisone), etoposide, mBACOD (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine and dexamethasone), PRO-MACE/MOPP
- 20 (prednisone, methotrexate (w/leucovin rescue), doxorubicin, cyclophosphamide, cisplatin, taxol, etoposide/mechlorethamine, vincristine, prednisone and procarbazine), vincristine, vinblastine, and the like as well as with radiation.

Total daily dose of the compositions of the invention to be administered to a human or other mammal host in single or divided doses may be in amounts, for example, from 0.0001 to 300 mg/kg body weight daily and more usually 1 to 300 mg/kg body weight.

- 30 It will be understood that agents which can be combined with the compound of the present invention for the inhibition, treatment or prophylaxis of angiogenic diseases are not limited to those listed above, but include in principle any agents useful for the treatment or prophylaxis of angiogenic diseases.

The peptides of the invention may be used for the development of affinity columns for isolation of receptors relevant to the antiangiogenic activity of the peptide of the invention, e.g. TSP-1 receptor, in, for example, cultured endothelial cells. As is known in the art, isolation and purification of the receptor may be followed by amino acid sequencing to identify and isolate polynucleotides which encode the receptor.

Recombinant expression of this receptor would allow greater amounts of receptor to be

produced, e.g. to produce a sufficient quantity for use in high throughput screening assays to identify other angiogenesis inhibitors.

The peptides of the present invention may be chemically coupled to isotopes, enzymes, carrier proteins, cytotoxic agents, fluorescent molecules, chemiluminescent, 5 bioluminescent and other compounds for a variety of applications. For example, a peptide may be labeled to facilitate testing of its ability to bind antisera or to detect cell types which possess a relevant receptor. The coupling technique is generally chosen on the basis of the functional groups available on the amino acids of the peptide including, but not limited to amino, sulfhydryl, carboxyl, amide, phenol, and imidazole. Various reagents 10 used to effect such couplings include among others, glutaraldehyde, diazodized benzidine, carbodiimide, and p-benzoquinone.

The efficiency of the coupling reaction is determined using different techniques appropriate for the specific reaction. For example, radiolabeling of the peptide with I¹²⁵ may be accomplished using chloramine T and NaI¹²⁵ of high specific activity. The 15 reaction is terminated with sodium metabisulfite and the mixture is desalted on disposable columns. The labeled peptide is eluted from the column and fractions are collected. Aliquots are removed from each fraction and radioactivity measured in a gamma counter. In this manner, a labeled peptide may be obtained which is free from unreacted NaI¹²⁵.

The peptides of the present invention can also be used as antigens to generate 20 polyclonal or monoclonal antibodies. Such antibodies can be used in diagnostic methods and kits to detect or quantify the peptide of the invention, or peptides related thereto, in a body fluid or tissue. Results from these tests could be used to diagnose or determine the prognostic relevance of such peptides.

The use of the peptides of the present invention to generate monoclonal antibodies 25 in animals such as the mouse, rabbit or sheep, follows techniques well known in the art. If desired, the antibodies can then be used to make anti-idiotype antibodies which in turn can be humanized as is known in the art to prevent immunological responses. The humanized antibodies can be used to inhibit angiogenesis or to make kits to detect the receptor as described herein.

For the production of polyclonal antisera in rabbits, sheep, goats or other animals 30 the peptides of the invention are coupled, for example through lysine residues, to purified bovine serum albumin using glutaraldehyde. The efficiency of this reaction may be determined by measuring the incorporation of radiolabeled peptide. Unreacted glutaraldehyde and peptide may be separated by dialysis and the conjugate stored for 35 subsequent use.

Serum samples from generation of polyclonal antisera or media samples from production of monoclonal antisera may be analyzed for determination of antibody titer and in particular, for the determination of high titer antisera. Subsequently, the highest titer antisera may be tested to establish the following: a) optimal antiserum dilution for highest specific binding of the antigen and lowest non-specific binding, b) ability to bind increasing amounts of peptide in a standard displacement curve, c) potential cross-reactivity with immunologically-related peptides and proteins (including plasminogen, TSP-1, and TSP-1 of related species), and d) ability to detect the peptide of the invention in extracts of plasma, urine, tissues, and in cell culture media.

Titer may be established through several means known in the art, such as by dot blot and density analysis, and also by precipitation of radiolabeled peptide-antibody complexes using protein A, secondary antisera, cold ethanol or charcoal-dextran followed by activity measurement with a gamma counter. If desired, the highest titer antisera may be purified on affinity columns. For example, the peptides of the invention may be coupled to a commercially available resin and used to form an affinity column. Antiserum samples may then be passed through the column so that antibodies to the peptides of the invention bind (via the peptide) to the column. These bound antibodies are subsequently eluted, collected and evaluated for determination of titer and specificity.

Kits for measurement of the compounds of the invention are also contemplated as part of the present invention. Antisera that possess the highest titer and specificity and can detect the peptides of the invention in extracts of plasma, urine, tissues, and in cell culture media may be used to establish assay kits for rapid, reliable, sensitive, and specific measurement and localization of peptides of the invention. These assay kits may employ (but are not limited to) the following techniques: competitive and non-competitive assays, radioimmunoassay (RIA), bioluminescence and chemiluminescence assays, fluorometric assays, sandwich assays, immunoradiometric assays, dot blots, enzyme linked assays including ELISA, microtiter plates, antibody coated strips or dipsticks for rapid monitoring of urine or blood, and immunocytochemistry. For each kit the range, sensitivity, precision, reliability, specificity and reproducibility of the assay are established by means well known to those skilled in the art.

The above described assay kit would provide instructions, antiserum, one or more peptides of the invention, and possibly radiolabeled peptides of the invention and/or reagents for precipitation of bound peptide/antibody complexes. Such a kit would be useful for the measurement of the peptide of the invention in biological fluids and tissue extracts of animals and humans with and without tumors, as is well known in the art.

Another kit may be used to visualize or localize the peptide of the invention in tissues and cells. Immunohistochemistry techniques and kits, for example, which employ such techniques are well known to those of ordinary skill in the art. Such a kit provides antisera to the peptide of the invention, and possibly blocking serum and secondary 5 antiserum linked to a fluorescent molecule such as fluorescein isothiocyanate, or to some other reagent used to visualize the primary antiserum. Using this methodology, biopsied tumors may be examined for sites of peptide production or for sites of the peptide receptor. Alternatively, a kit may supply radiolabeled nucleic acids for use in *in situ* hybridization to probe for messenger RNA which encodes the compound of the invention.

10

Synthesis of the Peptides

The polypeptides of the present invention may be synthesized by any techniques that are known to those skilled in the art. For solid phase peptide synthesis, a summary of the many techniques may be found in J.M. Stewart and J.D. Young, Solid Phase Peptide 15 Synthesis, W.H. Freeman Co. (San Francisco), 1963 and J. Meienhofer, Hormonal Proteins and Peptides, vol. 2, p. 46, Academic Press (New York), 1973. For classical solution synthesis see G. Schroder and K. Lupke, The Peptides, vol. 1, Academic Press (New York), 1965.

Reagents, resins, amino acids, and amino acid derivatives are commercially 20 available and can be purchased from Chem-Impex International, Inc. (Wood Dale, IL, U.S.A.) or Calbiochem-Novabiochem Corp. (San Diego, CA, U.S.A.) unless otherwise noted herein.

In general, these methods comprise the sequential addition of one or more amino acids or suitably protected amino acids to a growing peptide chain. Normally, either the 25 amino or carboxyl group of the first amino acid is protected by a suitable protecting group. The protected or derivatized amino acid can then be either attached to an inert solid support or utilized in solution by adding the next amino acid in the sequence having the complimentary (amino or carboxyl) group suitably protected, under conditions suitable for forming the amide linkage. The protecting group is then removed from this newly added 30 amino acid residue and the next amino acid (suitably protected) is then added, and so forth. After all the desired amino acids have been linked in the proper sequence, any remaining protecting groups (and any solid support) are removed sequentially or concurrently, to afford the final polypeptide. By simple modification of this general procedure, it is possible to add more than one amino acid at a time to a growing chain, for 35 example, by coupling (under conditions which do not racemize chiral centers) a protected tripeptide with a properly protected dipeptide to form, after deprotection, a pentapeptide.

A particularly preferred method of preparing compounds of the present invention involves solid phase peptide synthesis.

In this particularly preferred method the alpha-amino function is protected by an acid or base sensitive group. Such protecting groups should have the properties of being
5 stable to the conditions of peptide linkage formation, while being readily removable without destruction of the growing peptide chain or racemization of any of the chiral centers contained therein. Suitable protecting groups are 9-fluorenylmethyloxycarbonyl (Fmoc), *t*-butyloxycarbonyl (Boc), benzyloxycarbonyl (Cbz), biphenylisopropyl-oxycarbonyl, *t*-amyloxycarbonyl, isobornyloxycarbonyl, (α,α)-dimethyl-3,5-
10 dimethoxybenzyloxycarbonyl, o-nitrophenylsulfenyl, 2-cyano-*t*-butyloxycarbonyl, and the like. The 9-fluorenylmethyloxycarbonyl (Fmoc) protecting group is preferred.

Particularly preferred side chain protecting groups are, for side chain amino groups as in lysine and arginine: 2,2,5,7,8-pentamethylchroman-6-sulfonyl (pmc), nitro, p-toluenesulfonyl, 4-methoxybenzenesulfonyl, Cbz, Boc, and adamantyloxycarbonyl; for
15 tyrosine: benzyl, o-bromobenzyloxycarbonyl, 2,6-dichlorobenzyl, isopropyl, *t*-butyl (*t*-Bu), cyclohexyl, cyclopenyl and acetyl (Ac); for serine: *t*-butyl, benzyl and tetrahydropyranyl; for histidine: trityl, benzyl, Cbz, p-toluenesulfonyl and 2,4-dinitrophenyl; for tryptophan: formyl and Boc.

In the solid phase peptide synthesis method, the C-terminal amino acid is attached
20 to a suitable solid support or resin. Suitable solid supports useful for the above synthesis are those materials which are inert to the reagents and reaction conditions of the stepwise condensation-deprotection reactions, as well as being insoluble in the media used. The preferred solid support for synthesis of C-terminal carboxy peptides is 4-hydroxymethyl-phenoxy-methyl-copoly(styrene-1% divinylbenzene). The preferred solid support for C-terminal amide peptides is 4-(2',4'-dimethoxyphenyl-Fmoc-aminomethyl)phenoxy-acetamidoethyl resin available from Applied Biosystems.

The C-terminal amino acid is coupled to the resin by means of N,N'-dicyclohexylcarbodiimide (DCC), N,N'-diisopropylcarbodiimide (DIC) or O-benzotriazol-1-yl-N,N,N',N'-tetramethyluroniumhexafluorophosphate (HBTU), with or without 4-dimethylaminopyridine (DMAP), 1-hydroxybenzotriazole (HOBT), benzotriazol-1-yloxy-tris(dimethylamino)phosphoniumhexafluorophosphate (BOP) or bis(2-oxo-3-oxazolidinyl)phosphine chloride (BOPCl), mediated coupling for about 1 to about 24 hours at a temperature of between 10 ° and 50 °C in a solvent such as dichloromethane or DMF. When the solid support is 4-(2',4'-dimethoxyphenyl-Fmoc-aminomethyl)-
35 phenoxyacetamidoethyl resin, the Fmoc group is cleaved with a secondary amine, preferably piperidine, prior to coupling with the C-terminal amino acid as described above.

The preferred method for coupling to the deprotected 4-(2',4'-dimethoxyphenyl-Fmoc-aminomethyl)phenoxyacetamidoethyl resin is O-benzotriazol-1-yl-N,N,N',N'-tetramethyluroniumhexafluorophosphate (HBTU, 1 equiv.) and 1-hydroxybenzotriazole (HOBT, 1 equiv.) in DMF.

5 The coupling of successive protected amino acids can be carried out in an automatic polypeptide synthesizer as is well known in the art. In a preferred embodiment, the α -amino function in the amino acids of the growing peptide chain are protected with Fmoc. The removal of the Fmoc protecting group from the N-terminal side of the growing peptide is accomplished by treatment with a secondary amine, preferably piperidine. Each
10 protected amino acid is then introduced in about 3-fold molar excess and the coupling is preferably carried out in DMF. The coupling agent is normally O-benzotriazol-1-yl-N,N,N',N'-tetramethyluroniumhexafluorophosphate (HBTU, 1 equiv.) and 1-hydroxybenzotriazole (HOBT, 1 equiv.).

15 At the end of the solid phase synthesis, the polypeptide is removed from the resin and deprotected, either in succession or in a single operation. Removal of the polypeptide and deprotection can be accomplished in a single operation by treating the resin-bound polypeptide with a cleavage reagent, for example thianisole, water, ethanedithiol and trifluoroacetic acid.

20 In cases wherein the C-terminus of the polypeptide is an alkylamide, the resin is cleaved by aminolysis with an alkylamine. Alternatively, the peptide may be removed by transesterification, e.g. with methanol, followed by aminolysis or by direct transamidation. The protected peptide may be purified at this point or taken to the next step directly. The removal of the side chain protecting groups is accomplished using the cleavage cocktail described above.

25 The fully deprotected peptide is purified by a sequence of chromatographic steps employing any or all of the following types: ion exchange on a weakly basic resin in the acetate form; hydrophobic adsorption chromatography on underivitized polystyrene-divinylbenzene (for example, AMBERLITE[®] XAD); silica gel adsorption chromatography; ion exchange chromatography on carboxymethylcellulose; partition
30 chromatography, e.g. on SEPHADEX[®] G-25, LH-20 or countercurrent distribution; high performance liquid chromatography (HPLC), especially reverse-phase HPLC on octyl- or octadecylsilyl-silica bonded phase column packing.

35 The following examples will serve to further illustrate the preparation of the novel compounds of the invention.

Preparation of the Cleavage Reagent

The cleavage reagent (2 mL) is prepared by mixing, in the following order, thioanisole (100 μ L), water (50 μ L), ethanedithiol (50 μ L) and trifluoroacetic acid (1.8 mL). The freshly-prepared mixture is cooled to -5 °C to -10 °C and used as described below.

5

Cleavage and Deprotection Procedure

A mixture of resin-bound polypeptide and cleavage reagent is stirred at 0 °C for 10-15 minutes and then at ambient temperature for a further 1.75 hours. The amount of time is increased by 0.5 hours for each additional arginine up to a total of three hours. The 10 amount of cleavage reagent used is determined using the following formula:

weight of resin (mg)	amount of cleavage reagent (μ L)
0-10	100
10-25	200
25-50	400
50-100	700
100-200	1200

The resin is then filtered off and rinsed with neat trifluoroacetic acid. The filtrate is then added in 0.5 mL portions to a centrifuge tube containing about 8 mL of cold diethyl ether. The suspension is then centrifuged and the supernatant is decanted off. The pellet 15 is re-suspended in about 8 mL of ether, another 0.5 mL of the filtrate is added, and the process is repeated until all of the peptide is precipitated. The precipitated filtrate is then washed with ether, dried and lyophilized.

If the peptide does not precipitate upon addition to ether, the mixture is shaken with aqueous 30% acetic acid. The organic phase is then extracted twice with aqueous 20 30% acetic acid and the combined aqueous extracts are lyophilized.

Example 1



In the peptide synthesis column position of a Perkin Elmer/Applied Biosynthesis 25 SYNERGY® peptide synthesizer is placed an Pro(2-CITrT) peptide synthesis column (25 μ M amino acid; Nova Biochem). Amino acids are added sequentially according to the following synthetic cycle:

- (1) Solvating the resin using DMF for about 5 minutes;
- (2) Washing with DMF for about 5 minutes;

(3) Activating the incoming Fmoc protected amino acid (75 μ M) using a 0.2 M solution of HBTU (75 μ M) and HOBT (75 μ M) in DMSO-NMP (N-methylpyrrolidone);

5 (4) Coupling using a solution in DMF of the activated Fmoc protected amino acid prepared in step 3 above for about 30 minutes;

(5) Washing with DMF for 5 minutes; and

(6) For peptides capped with acetyl at the N-terminus, substituting acetic acid (87 μ M) for an Fmoc protected amino acid and using 87 μ M each of HBTU and HOBT.

10 (7) For peptides capped with ethylamide at the C-terminus, adding DMF to the resin followed by ByProp (1.1 equivalents) and ethylamine (20 equivalents) in THF.

The amino acids were coupled to the resin in the following order using the conditions indicated.

<u># Amino Acid</u>	<u>Coupling</u>
1. Fmoc-Arg(Pmc)	30 minutes
2. Fmoc-Ile	30 minutes
3. Fmoc-Nva	30 minutes
4. Fmoc-Thr(<i>t</i> -Bu)	30 minutes
5. Fmoc-D-Ile	30 minutes
6. Fmoc-Val	30 minutes
7. Fmoc-Gly	30 minutes
8. Fmoc-Sar	30 minutes

15 Upon completion of the synthesis, the resin was washed with THF for about 5 minutes to remove DMF and shrink the resin. The resin was then gas dried with argon for about 10 minutes and nitrogen for a further 10 minutes to provide the resin-bound peptide (85 mg). Cleavage and deprotection are accomplished using the procedure described above (40 mg of dry resin-bound peptide, 700 μ L of cleavage reagent, cleavage time 2.5 hours) to give the crude peptide (14 mg). Purification by HPLC using a 7 μ m Symmetry Prep C18 column (7.8x300 mm) with solvent mixtures varying in a gradient from 5% to 100% acetonitrile-water over a period of 50 minutes followed by lyophilization provided the desired peptide.

20 The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 26.5 min (10% to 40% acetonitrile in water containing 0.01% of TFA, over 30 min period); MS (ESI) m/e 994 (M+H)⁺.

Example 2
 pyroGlu-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

# Amino Acid	Coupling
1. Fmoc-Arg(Pmc)	30 minutes
2. Fmoc-Ile	30 minutes
3. Fmoc-Nva	30 minutes
4. Fmoc-Thr(<i>t</i> -Bu)	30 minutes
5. Fmoc-D-Ile	30 minutes
6. Fmoc-Val	30 minutes
7. Fmoc-Gly	30 minutes
8. pyroGlu(Boc)	30 minutes

5 The desired peptide was prepared using the conditions described for Example 1.
 The amino acids were coupled to the resin in the following order using the conditions indicated.

10 The pure fractions were lyophilized to yield pyroGlu-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 23.5 min (gradient of 10% to 40% acetonitrile in water containing 0.01% of TFA, over 30 min period); MS (ESI) m/e 994 (M+H)⁺.

Example 3

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₃

15 The procedure described in Example 1 was used but substituting methylamine (2.0 M solution in THF) for ethylamine. After cleavage of the peptide from the resin and removal of the protecting groups the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₃ as the trifluoroacetate salt: R_t = 3.224 min (gradient of 20% to 95% acetonitrile in water containing 0.01 M NH₄Ac over 10 min period); MS (ESI) m/e 930 (M+H)⁺; Amino Acid Anal.: 1.09 Sar; 1.03 Gly; 0.98 Val; 0.98 Ile; 0.54 Thr; 1.72 Nva; 1.01 Arg; 1.08 Pro.

Example 4

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH(CH₃)₂

25 The procedure described in Example 1 was used but substituting isopropylamine for ethylamine. After cleavage of the peptide from the resin and removal of the protecting

groups the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHIsopropyl as the trifluoroacetate salt: R_t = 3.648 min (gradient of 20% to 95% acetonitrile in water containing 0.01 M NH₄Ac over 10 min period); MS (ESI) m/e 1008 (M+H)⁺; Amino Acid Anal.: 1.10 Sar; 0.99 Gly; 0.96 Val; 1.88 Ile; 0.56 Thr; 1.67 Nva; 0.96 Arg; 1.09 Pro.

Example 5

10 N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHethyl-(1-pyrrolidine)

Resin Preparation

4-(4-Formyl-3-methoxyphenoxy)butyryl AM resin (0.5 g, 0.54 mmol/g substitution) was placed in a solid phase synthesis reaction vessel containing (9:1) DMA/acetic acid (4 mL). The mixture was shaken for 5 min. The resin was drained and this process was repeated three times. To the swollen resin were added 10-15 grains of activated 4A molecular sieves and (9:1) DMA/acetic acid (4mL) and 10 molar equivalents of 1-(2-aminoethyl)pyrrolidine. The slurry was shaken for 1h at rt and to it was added 10 molar equivalents of sodium triacetoxyborohydride. The slurry was shaken for 2 h at rt. The resin was drained and washed three times with DMA, three times with methanol, three times with dichloromethane, three times with diethyl ether and dried in vacuo at rt overnight. The dry resin was swollen in DMA (4 mL) and shaken for 5 min. This process was repeated twice.

Coupling of Fmoc-Pro

25 To the swollen resin in the reaction vessel were added sequentially the following chemicals: DMA (4 mL), one equivalent of DIEA, a DMA solution containing 3.0 equivalents of Fmoc-Pro, 3.0 equivalents of HATU, and 3.0 equivalents of DIEA. The slurry was shaken overnight. The resin was drained and washed three times with DMA, three times with methanol, three times with dichloromethane, three times with diethyl ether and dried in vacuo at rt overnight. A small portion of the resin was used to determine the Fmoc-Pro loading. The rest of the resin was shaken with DMA (4 mL) three times for 5 min and then for 1 h at rt with a solution of (8:1:1) DMA/pyridine/acetic anhydride (5 mL). The resin was drained and washed three times with DMA, three times with methanol, three times with dichloromethane, and three times with diethyl ether. The resin was dried in vacuo at rt overnight and then used in the subsequent solid phase peptide synthesis.

Synthesis of above peptide

In the synthesis of the above peptide the amino acids, the coupling conditions and the synthetic protocol used were the identical to as those described in Example 1. Upon completion of the synthesis the peptide and the protecting groups were cleaved at rt using (95:5) TFA/anisole (3 mL) for 3h. The resin was filtered and washed three times with methanol. The combined filtrates were concentrated in vacuo and to the residue was added diethylether. The solid precipitate was filtered. The crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHethyl(1-pyrrolidine) as the bis-trifluoroacetate salt: $R_t = 4.40$ min (gradient of 20% to 95% acetonitrile in water containing 0.01 M NH₄Ac over 10 min period); MS (ESI) m/e 1063 (M+H)⁺; Amino Acid Anal.: 0.95 Sar; 1.0 Gly; 0.86 Val; 1.63 Ile; 0.56 Thr; 1.38 Nva; 0.88 Arg; 1.07 Pro.

15

Example 6

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHethyl(1-piperidine)

The procedure described in Example 5 was used but substituting 1-(2-aminoethyl)piperidine for 1-(2-aminoethyl)pyrrolidine in the reductive alkylation step. After cleavage of the peptide from the resin and removal of the protecting groups the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHethyl(1-piperidine) as the bis-trifluoroacetate salt: $R_t = 4.437$ min (gradient of 20% to 95% acetonitrile in water containing 0.01 M NH₄Ac over 10 min period); MS (ESI) m/e 1077 (M+H)⁺; Amino Acid Anal.: 1.11 Sar; 1.04 Gly; 0.99 Val; 1.77 Ile; 0.61 Thr; 1.61 Nva; 0.97 Arg; 1.10 Pro.

Example 7

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHmethylcyclopropyl

The procedure described in Example 1 was used but substituting (aminoethyl)cyclopropane for 1-(2-aminoethyl)pyrrolidine). After cleavage of the peptide from the resin and removal of the protecting groups the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHmethylcyclopropyl as the trifluoroacetate

salt: $R_t = 3.815$ min (gradient of 20% to 95% acetonitrile in water containing 0.01 M NH₄Ac over 10 min period); MS (ESI) m/e 1020 (M+H)⁺; Amino Acid Anal.: 1.01 Sar; 0.96 Gly; 0.96 Val; 1.66 Ile; 0.53 Thr; 1.65 Nva; 1.08 Arg; 1.09 Pro.

5

Example 8

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHethyl-1-(R)-cyclohexyl

The procedure described in Example 5 was used but substituting (R)-1-cycloxyethylamine for 1-(2-aminoethylpyrrolidine). After cleavage of the peptide from the resin and removal of the protecting groups the crude product was purified by C-18 column chromatography using solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHethyl-1-(R)-cyclohexyl as the trifluoroacetate salt: $R_t = 5.196$ min (gradient of 20% to 95% acetonitrile in water containing 0.01 M NH₄Ac over 10 min period); MS (ESI) m/e 1076 (M+H)⁺; Amino Acid Anal.: 1.19 Sar; 0.99 Gly; 0.62 Val; 1.47 Ile; 0.48 Thr; 1.57 Nva; 1.01 Arg; 0.83 Pro.

10

15

Example 9

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNH(2-hydroxyethyl)

The procedure described in Example 5 was used but substituting O-TBDMS-ethanolamine for 1-(2-aminoethylpyrrolidine). After cleavage of the peptide from the resin and removal of the protecting groups the crude product was purified by C-18 column chromatography using solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNH(2-hydroxyethyl) as the trifluoroacetate salt: $R_t = 4.04$ min (gradient of 20% to 95% acetonitrile in water containing 0.01 M NH₄Ac over 10 min period); MS (ESI) m/e 1010 (M+H)⁺; Amino Acid Anal.: 1.04 Sar; 1.01 Gly; 0.98 Val; 1.59 Ile; 0.44 Thr; 1.45 Nva; 0.99 Arg; 1.06 Pro.

20

25

Example 10

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNH₂

The procedure described in Example 1 was used but substituting Fmoc-Pro-Sieber amide resin for H-Pro-2-ClTrt resin. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL), the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNH₂ as the

trifluoroacetate salt: $R_t = 4.063$ min (gradient of 20% to 95% acetonitrile in water containing 0.01 M NH₄Ac over 10 min period); MS (ESI) m/e 966 (M+H)⁺; Amino Acid Anal.: 0.87 Sar; 0.98 Gly; 0.94 Val; 1.73 Ile; 0.47 Thr; 1.35 Nva; 1.02 Arg; 1.05 Pro.

5

Example 11

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₂OCH₃

The procedure described in Example 5 was used but substituting 2-methoxyethylamine for 1-(2-aminoethylpyrrolidine). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₂OCH₃ as the trifluoroacetate salt: $R_t \approx 3.40$ min (gradient of 20% to 95% acetonitrile in water containing 0.01 M NH₄Ac over 10 min period); MS (ESI) m/e 1024 (M+H)⁺; Amino Acid Anal.: 1.02 Sar; 1.06 Gly; 0.97 Val; 1.54 Ile; 0.47 Thr; 1.81 Nva; 0.97 Arg; 1.25 Pro.

20

Example 12

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₂-cyclohexyl

The procedure described in Example 5 was used but substituting cyclohexylethylamine for 1-(2-aminoethylpyrrolidine). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₂-cyclohexyl as the trifluoroacetate salt: $R_t = 4.97$ min (gradient of 20% to 95% acetonitrile in water containing 0.01 M NH₄Ac over 10 min period); MS (ESI) m/e 1076 (M+H)⁺; Amino Acid Anal.: 0.87 Sar; 1.00 Gly; 0.88 Val; 1.34 Ile; 0.44 Thr; 1.61 Nva; 1.07 Arg; 1.05 Pro.

30

Example 13

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₂CH₃

The procedure described in Example 1 was used but substituting propylamine for ethylamine. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-

water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₂CH₃ as the trifluoroacetate salt: R_t = 3.68 min (gradient of 20% to 95% acetonitrile in water containing 0.01 M NH₄Ac over 10 min period); MS (ESI) m/e 1008 (M+H)⁺; Amino Acid Anal.: 0.94 Sar; 1.09 Gly; 0.96 Val; 5 1.58 Ile; 0.51 Thr; 1.78 Nva; 0.96 Arg; 1.23 Pro.

Example 14

N-Ac-Sar-Gly-Val-D-alloIle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-D-alloIle 10 for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield 15 N-Ac-Sar-Gly-Val-D-alloIle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 22.5 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 994 (M+H)⁺; Amino Acid Anal.: 0.95 Sar; 0.96 Gly; 0.97 Val; 0.99 Ile; 0.54 Thr; 1.66 Nva; 1.14 Arg; 1.08 Pro.

Example 15

N-Ac-Sar-Gly-Val-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-D-Leu for 20 Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly- 25 Val-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.54 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 994 (M+H)⁺; Amino Acid Anal.: 1.00 Sar; 0.93 Gly; 0.96 Val; 1.02 Leu; 0.58 Thr; 1.50 Nva; 0.99 Ile; 1.14 Arg; 1.08 Pro.

30

Example 16

N-Ac-Sar-Gly-Val-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-Ile for 35 Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-

water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.28 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 994 (M+H)⁺; Amino Acid Anal.: 0.95 Sar; 0.94 Gly; 0.89 Val; 1.70 Ile; 5 0.52 Thr; 1.67 Nva; 0.99 Ile; 1.27 Arg; 1.06 Pro.

Example 17

N-Ac-Sar-Gly-Val-Gly-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-Gly for 10 Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-Gly-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 2.47 min 15 (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 938 (M+H)⁺; Amino Acid Anal.: 1.10 Sar; 1.94 Gly; 1.03 Val; 0.98 Ile; 0.54 Thr; 1.61 Nva; 1.28 Arg; 1.05 Pro.

Example 18

N-Ac-Sar-Gly-Val-D-Val-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-D-Val for 20 Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-25 Val-D-Val-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.13 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 980 (M+H)⁺; Amino Acid Anal.: 1.07 Sar; 1.0 Gly; 2.01 Val; 0.99 Ile; 0.62 Thr; 1.54 Nva; 1.49 Arg; 1.11 Pro.

30

Example 19

N-Ac-Sar-Gly-Val-alloIle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-alloIle for 35 Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-

water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-alloIle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 4.174 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 994 (M+H)⁺; Amino Acid Anal.: 1.02 Sar; 0.99 Gly; 0.95 Val; 1.29 Ile;

5 0.45 Thr; 1.52 Nva; 1.54 Arg; 1.07 Pro.

Example 20

N-Ac-Sar-Gly-Val-D-Ala-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-D-Ala for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ala-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.826 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (APCI) m/e 952 (M)⁺ and 908 (M-44)⁺.

Example 21

N-Ac-Sar-Gly-Val-D-Lys-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-Lys(Boc) for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Lys-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.544 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (APCI) m/e 1009 (M)⁺ and 965 (M-44)⁺.

Example 22

N-Ac-Sar-Gly-Val-D-Met-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-D-Met for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Met-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 4.141 min

(gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period);
MS (APCI) m/e 1012 (M)⁺.

Example 23

5 N-Ac-Sar-Gly-Val-D-Nle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-D-Nle for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-
10 water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-
Val-D-Nle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 4.383 min
(gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period);
MS (APCI) m/e 994 (M)⁺.

15 Example 24

N-Ac-Sar-Gly-Val-D-Phe-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-D-Phe for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column
20 chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-
water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-
Val-D-Phe-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 4.476 min
(gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period);
MS (APCI) m/e 1028 (M)⁺.

25 Example 25

N-Ac-Sar-Gly-Val-D-Trp-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

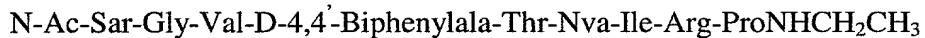
The procedure described in Example 1 was used but substituting Fmoc-D-Trp(Boc)
for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting
30 groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column
chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-
water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-
Val-D-Trp-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt:
R_t = 4.430 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over
35 30 min period); MS (APCI) m/e 1024 (M)⁺.

Example 26



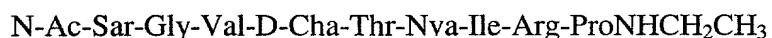
The procedure described in Example 1 was used but substituting Fmoc-D-Tyr(2-CITrt) for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Tyr-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.964 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (APCI) m/e 1045 (M)⁺.

Example 27



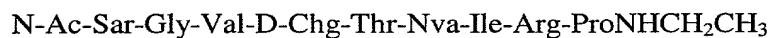
The procedure described in Example 1 was used but substituting Fmoc-D-4,4'-Biphenylala for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-4,4'-Biphenylala -Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 5.005 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (APCI) m/e 1104 (M)⁺.

Example 28



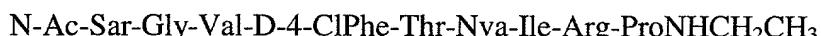
The procedure described in Example 1 was used but substituting Fmoc-D-Cha for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Cha-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 5.005 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (APCI) m/e 1034 (M)⁺.

Example 29



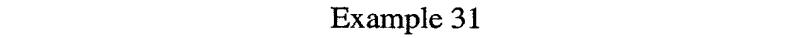
The procedure described in Example 1 was used but substituting Fmoc-D-Chg for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Chg-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 4.377 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (APCI) m/e 977 (M)⁺.

10 Example 30



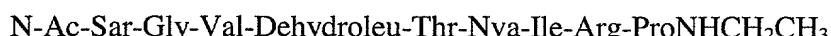
The procedure described in Example 1 was used but substituting Fmoc-D-4-ClPhe for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-4-ClPhe-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_f = 4.674 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (APCI) m/e 1018 (M)⁺.

20



The procedure described in Example 1 was used but substituting Fmoc-D-Hphe for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Hphe-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 4.597 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (APCI) m/e 1042 (M)⁺ and 998 (M-44)⁺

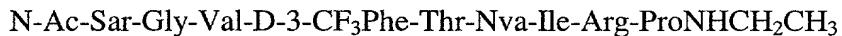
Example 32



The procedure described in Example 1 was used but substituting Fmoc-Dehydroleu
 35 for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting
 groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column

chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-Dehydroleu-Thr-Nva-Ile-Arg-ProNH₂CH₃ as the trifluoroacetate salt: R_t = 4.1707 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (APCI) m/e 992 (M)⁺ and 949 (M-44)⁺.

5 Example 33



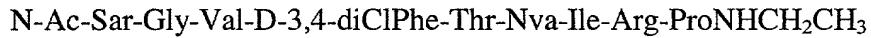
The procedure described in Example 1 was used but substituting Fmoc-D-3-CF₃Phe for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-3-CF₃Phe-Thr-Nva-Ile-Arg-ProNH₂CH₃ as the trifluoroacetate salt: R_t = 4.825 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (APCI) m/e 1097 (M)⁺ and 1053 (M-44)⁺.

10 Example 34



20 The procedure described in Example 1 was used but substituting Fmoc-D-pentaFPhe for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-pentaFPhe-Thr-Nva-Ile-Arg-ProNH₂CH₃ as the trifluoroacetate salt: R_t = 4.810 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (APCI) m/e 1118 (M)⁺ and 1075 (M-44)⁺.

30 Example 35



The procedure described in Example 1 was used but substituting Fmoc-D-3,4-diClPhe for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield

N-Ac-Sar-Gly-Val-D-3,4-diClPhe-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 4.911 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (APCI) m/e 1100 (M+3)⁺.

5

Example 36

N-Ac-Sar-Gly-Val-D-3-ClPhe-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-D-3-ClPhe for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-3-ClPhe-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 4.689 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (APCI) m/e 1062 (M)⁺.

Example 37

N-Ac-Sar-Gly-Val-D-2-Thienylala-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-D-2-Thienylala for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-2-Thienylala-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 4.388 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (APCI) m/e 1034 (M)⁺.

Example 38

N-Ac-Sar-Gly-Val-D-3-CNphe-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-D-3-CN-Phe for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield

N-Ac-Sar-Gly-Val-D-3-CNPhe-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 4.361 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (APCI) m/e 1009 (M)⁺.

5

Example 39

N-Ac-Sar-Gly-Val-D-3,3-Diphenylala-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-D-3,3-Diphenylala for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-3,3'-Diphenylala-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 4.778 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (APCI) m/e 1104 (M)⁺.

15

Example 40

N-Ac-Sar-Gly-Val-D-3-Benzothienylala-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-D-3-Benzothienylala for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-3-Benzothienylala-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 4.797 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (APCI) m/e 1084 (M)⁺.

Example 41

N-Ac-Sar-Gly-Val-D-3,4-diF-Phe-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-D-3,4-diF-Phe for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-3,4-diF-Phe-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 4.608 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (APCI) m/e 1064 (M)⁺.

Example 42

N-Ac-Sar-Gly-Val-D-Ile-Thr-DNva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-DNva for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-DNva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.75 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 994 (M+H)⁺; Amino Acid Anal.: 1.08 Sar; 0.96 Gly; 0.95 Val; 1.74 Ile; 0.50 Thr; 1.69 Nva; 1.26 Arg; 1.09 Pro.

Example 43

N-Ac-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-Gln(Trt) for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.047 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1023 (M+H)⁺; Amino Acid Anal.: 1.15 Sar; 0.96 Gly; 0.63 Val; 1.7 Ile; 0.46 Thr; 0.65 Glu; 1.45 Arg; 1.04 Pro.

Example 44

N-Ac-Sar-Gly-Val-D-Ile-Thr-Cha-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-Cha for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Cha-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 4.503 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1048 (M+H)⁺; Amino Acid Anal.: 1.18 Sar; 0.94 Gly; 0.59 Val; 1.65 Ile; 0.45 Thr; 0.37 Cha; 1.45 Arg; 1.06 Pro.

Example 45

N-Ac-Sar-Gly-Val-D-Ile-Thr-Gly-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-Gly for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Gly-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.11 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period);
MS (ESI) m/e 952 (M+H)⁺.

Example 46

N-Ac-Sar-Gly-Val-D-Ile-Thr-Ala-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-Ala for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Ala-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.16 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 966 (M+H)⁺.

Example 47

N-Ac-Sar-Gly-Val-D-Ile-Thr-Val-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-Val for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Val-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.36 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 994 (M+H)⁺.

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Example 48

N-Ac-Sar-Gly-Val-D-Ile-Thr-Abu-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-Abu for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Abu-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.23 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 980 (M+H)⁺.

10 Example 49



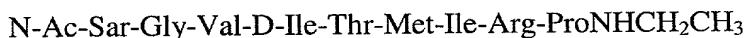
The procedure described in Example 1 was used but substituting Fmoc-Allylgly for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Allylgly-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.40 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 992 (M+H)⁺.

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The procedure described in Example 1 was used but substituting Fmoc-Octylgly for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Octylgly-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 5.30 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1064 (M+H)⁺.

Example 51



The procedure described in Example 1 was used but substituting Fmoc-Met for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column

chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Met-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.48 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period);
5 MS (ESI) m/e 1027 (M+H)⁺.

Example 52

N-Cyclohexylacetyl-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting cyclohexylacetic acid for acetic acid. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Cyclohexylacetyl-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 5.11 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1076 (M+H)⁺; Amino Acid Anal.: 1.15 Sar; 0.97 Gly; 0.95 Val; 1.79 Ile; 0.54 Thr; 1.66 Nva; 1.28 Arg; 1.08 Pro.

Example 53

N-(2-Me-Nicotinyl)-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting 2-Me-nicotinic acid for acetic acid. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-(2-Me-Nicotinyl)-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 5.11 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1071 (M+H)⁺; Amino Acid Anal.: 1.19 Sar; 1.01 Gly; 0.99 Val; 1.79 Ile; 0.57 Thr; 1.70 Nva; 1.59 Arg; 1.17 Pro.

Example 54

N-Succinyl-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but acylating the peptide resin (after the Fmoc-Sar coupling and deprotection) with a (1:1) succinic anhydride/pyridine mixture (2 mL) overnight. After washing the resin and cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude

product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Succinyl-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 2.72 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1052 (M+H)⁺; Amino Acid Anal.: 1.16 Sar; 1.05 Gly; 0.95 Val; 1.85 Ile; 0.57 Thr; 1.70 Nva; 1.59 Arg; 1.17 Pro.

5 Example 55

N-Nicotinyl-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting nicotinic acid for acetic acid at the last coupling. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Nicotinyl-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.6 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1057 (M+H)⁺; Amino Acid Anal.: 1.03 Sar; 0.89 Gly; 0.81 Val; 1.48 Ile; 0.40 Thr; 1.46 Nva; 1.07 Arg; 1.04 Pro.

20 Example 56

N-Propionyl-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting propionic acid for acetic acid at the last coupling. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Propionyl-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.7 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1008 (M+H)⁺; Amino Acid Anal.: 0.93 Sar; 0.97 Gly; 0.88 Val; 1.60 Ile; 0.44 Thr; 1.58 Nva; 1.17 Arg; 1.10 Pro.

30

Example 57

N-MeOacetyl-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting methoxyacetic acid for acetic acid at the last coupling. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of

10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-MeOacetyl-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.45 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1024 (M+H)⁺; Amino Acid
5 Anal.: 1.12 Sar; 1.06 Gly; 0.94 Val; 1.62 Ile; 0.48 Thr; 1.91 Nva; 1.40 Arg; 1.27 Pro.

Example 58

N-Shikimyl-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting shikimic acid for acetic acid at the last coupling. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Shikimyl-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt:
10 R_t = 3.0 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1108 (M+H)⁺; Amino Acid Anal.: 1.22 Sar; 1.06 Gly; 0.94 Val; 1.80 Ile; 0.55 Thr; 1.70 Nva; 1.28 Arg; 1.26 Pro.
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Example 59

N-(2-Furoyl)-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting 2-furoic acid for acetic acid at the last coupling. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-(2-Furoyl)-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt:
20 R_t = 4.0 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1046 (M+H)⁺; Amino Acid Anal.: 1.02 Sar; 1.00 Gly; 0.99 Val; 1.66 Ile; 0.45 Thr; 1.75 Nva; 1.45 Arg; 1.21 Pro.
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Example 60

N-Butyryl-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting butyric acid for acetic acid at the last coupling. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50%
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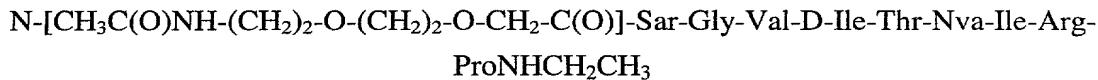
acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Butyryl-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_f = 4.03 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1022 (M+H)⁺; Amino Acid Anal.: 1.13 Sar; 0.99 Gly; 1.01 Val; 1.93 Ile; 0.67 Thr; 1.61 Nva; 1.45 Arg; 1.08 Pro.

Example 61



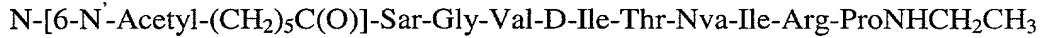
The procedure described in Example 1 was used but substituting tetrahydro-2-furoic acid for acetic acid at the last coupling. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-(tetrahydro-2furoyl)-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNH₂CH₂CH₃ as the trifluoroacetate salt: R_f = 3.91 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1050 (M+H)⁺; Amino Acid Anal.: 1.12 Sar; 0.97 Gly; 0.88 Val; 1.41 Ile; 0.42 Thr; 1.60 Nva; 1.43 Arg; 1.03 Pro.

Example 62



The procedure described in Example 1 was used but coupling with Fmoc-8-amino-3,6-dioxo-octanoic acid after the Fmoc-Sar coupling, after removal of the terminal Fmoc the peptide resin was coupled with acetic acid as described above. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-[CH₃C(O)NH-(CH₂)₂-O-(CH₂)₂-O-CH₂-C(O)]-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.32 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1139 (M+H)⁺; Amino Acid Anal.: 1.04 Sar; 1.01 Gly; 0.91 Val; 1.67 Ile; 0.53 Thr; 1.77 Nva; 1.39 Arg; 1.02 Pro.

Example 63



The procedure described in Example 1 was used but coupling with Fmoc-6-amino-hexanoic acid after the Fmoc-Sar coupling, after removal of the terminal Fmoc the peptide resin was coupled with acetic acid as described above. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole

5 (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-[6-N'-Acetyl-(CH₂)₅C(O)]-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.60 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1107 (M+H)⁺; Amino Acid Anal.: 1.13 Sar; 0.96 Gly; 0.89 Val; 1.42 Ile; 0.43 Thr; 1.68 Nva; 1.44 Arg; 1.04 Pro.

Example 64

N-Hexanoyl-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

15 The procedure described in Example 1 was used but substituting hexanoic acid for acetic acid. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Hexanoyl-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 4.95 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1050 (M+H)⁺; Amino Acid Anal.: 1.07 Sar; 0.93 Gly; 1.02 Val; 1.95 Ile; 0.56 Thr; 1.31 Nva; 1.52 Arg; 1.05 Pro.

Example 65

N-[4-N'-Acetyl-butyryl]-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but coupling with Fmoc-4-amino-butyric acid after the Fmoc-Sar coupling, after removal of the terminal Fmoc the peptide resin was coupled with acetic acid as described above. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-[4-N'-Acetyl-butyryl]-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 4.09 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1079

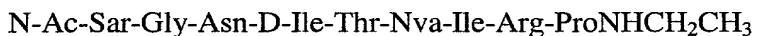
(M+H)⁺; Amino Acid Anal.: 1.03 Gaba; 1.07 Sar; 0.93 Gly; 1.00 Val; 1.90 Ile; 0.54 Thr; 1.30 Nva; 1.54 Arg; 1.06 Pro.

Example 66



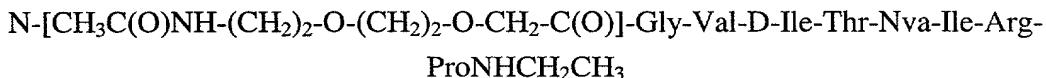
The procedure described in Example 1 was used but omitting the acetic acid coupling at the end. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield H-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the bistrifluoroacetate salt: R_t = 3.65 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 952 (M+H)⁺; Amino Acid Anal.: 1.00 Sar; 1.00 Gly; 0.99 Val; 1.67 Ile; 0.50 Thr; 1.76 Nva; 1.47 Arg; 1.22 Pro.

15 Example 67



The procedure described in Example 1 was used but substituting Fmoc-Asn(Trt) for Fmoc-Val. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Asn-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the bistrifluoroacetate salt: R_t = 2.45 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1009 (M+H)⁺; Amino Acid Anal.: 1.05 Sar; 0.98 Gly; 0.96 Asp; 1.7 Ile; 0.48 Thr; 1.54 Nva; 1.32 Arg; 1.07 Pro.

Example 68



The procedure described in Example 1 was used but substituting Fmoc-8-amino-3,6-dioxo-octanoic acid for Fmoc-Sar. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-[CH₃C(O)NH-(CH₂)₂-O-(CH₂)₂-O-CH₂-C(O)]-Gly-Val-D-Ile-Thr-

Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 4.12 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1068 (M+H)⁺; Amino Acid Anal.: 0.93 Gly; 1.02 Val; 1.97 Ile; 0.57 Thr; 1.31 Nva; 1.54 Arg; 1.05 Pro.

5

Example 69

N-Ac-Pro-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-Pro for Fmoc-Sar. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Pro-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 4.30 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1020 (M+H)⁺; Amino Acid Anal.: 0.92 Gly; 0.99 Val; 1.80 Ile; 0.50 Thr; 1.32 Nva; 1.53 Arg; 2.09 Pro.

Example 70

N-Ac-Gly-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-Gly for Fmoc-Sar. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Gly-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 4.08 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 980 (M+H)⁺; Amino Acid Anal.: 1.89 Gly; 1.02 Val; 1.91 Ile; 0.52 Thr; 1.35 Nva; 1.57 Arg; 1.09 Pro.

30

Example 71

N-Ac-Ala-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-Ala for Fmoc-Sar. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Ala-Gly-

Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 4.00 min
(gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period);
MS (ESI) m/e 994 (M+H)⁺; Amino Acid Anal.: 1.01 Ala; 0.93 Gly; 1.01 Val; 1.92 Ile;
0.56 Thr; 1.30 Nva; 1.51 Arg; 1.05 Pro.

5

Example 72

N-Ac-NEtGly-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-NEtGly for
Fmoc-Sar. After cleavage of the peptide from the resin and removal of the protecting
10 groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column
chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-
water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-NEtGly-
Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 4.24 min
(gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period);
15 MS (ESI) m/e 1008 (M+H)⁺; Amino Acid Anal.: 0.95 Gly; 1.04 Val; 1.99 Ile; 0.59 Thr;
1.34 Nva; 1.50 Arg; 1.01 Pro.

20

Example 73

N-Ac-Sar-Gly-Val-D-Ile-Thr-Leu-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-Leu for
Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting
25 groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column
chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-
water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-
Val-D-Ile-Thr-Leu-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 4.348 min
(gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period);
30 MS (ESI) m/e 1008 (M+H)⁺; Amino Acid Anal.: 0.88 Sar; 0.99 Gly; 0.95 Val; 1.03 Ile;
0.55 Thr; 1.12 Leu; 1.53 Arg; 1.07 Pro.

Example 74

N-Ac-Sar-Gly-Val-D-Ile-Thr-Ser-Ile-Arg-ProNHCH₂CH₃

35 The procedure described in Example 1 was used but substituting Fmoc-Ser(tBu)
for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting

groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield

N-Ac-Sar-Gly-Val-D-Ile-Thr-Ser-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt:

5 R_t = 3.963 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 982 (M+H)⁺; Amino Acid Anal.: 0.91 Sar; 0.97 Gly; 1.00 Val; 1.03 Ile; 0.56 Thr; 0.23 Ser; 1.52 Arg; 1.08 Pro.

Example 75

10 N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Pro-D-AlaNH₂

The procedure described in Example 10 was used but substituting Fmoc-D-Ala-Sieber amide resin for Fmoc-Pro-Sieber amide resin. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Pro-D-AlaNH₂ as the trifluoroacetate salt: R_t = 4.117 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1037 (M+H)⁺; Amino Acid Anal.: 0.85 Sar; 0.94 Gly; 0.92 Val; 1.83 Ile; 0.54 Thr; 1.18 Nva; 1.01 Arg; 1.04 Pro; 1.01 Ala.

Example 76

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-D-ProNHCH₂CH₃

The procedure described in Example 10 was used but substituting Fmoc-D-Pro-Sieber ethylamide resin for Fmoc-Pro-Sieber amide resin. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-D-Pro-NHCH₂CH₃ as the trifluoroacetate salt: R_t = 4.20 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 994 (M+H)⁺.

Example 77

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-AbuNHCH₂CH₃

35 The procedure described in Example 10 was used but substituting Fmoc-Abu-Sieber ethylamide resin for Fmoc-Pro-Sieber amide resin. After cleavage of the peptide

from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-AbuNHCH₂CH₃ as the trifluoroacetate salt: R_t = 4.35 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 982 (M+H)⁺.

5
Example 78

10 N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-PheNHCH₂CH₃

The procedure described in Example 10 was used but substituting Fmoc-Phe-Sieber ethylamide resin for Fmoc-Pro-Sieber amide resin. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Phe-NHCH₂CH₃ as the trifluoroacetate salt: R_t = 4.73 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1044 (M+H)⁺.

20
Example 79

20 N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Tic-NHCH₂CH₃

The procedure described in Example 10 was used but substituting Fmoc-Tic-Sieber ethylamide resin for Fmoc-Pro-Sieber amide resin. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Tic-NHCH₂CH₃ as the trifluoroacetate salt: R_t = 4.68 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1056 (M+H)⁺.

30
Example 80

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Hyp-NHCH₂CH₃

The procedure described in Example 10 was used but substituting Fmoc-Hyp-Sieber ethylamide resin for Fmoc-Pro-Sieber amide resin. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure

fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Hyp-NHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.95 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1010 (M+H)⁺.

5

Example 81

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Aib-NHCH₂CH₃

The procedure described in Example 10 was used but substituting Fmoc-Aib-Sieber ethylamide resin for Fmoc-Pro-Sieber amide resin. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Aib-NHCH₂CH₃ as the trifluoroacetate salt: R_t = 4.25 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 982 (M+H)⁺.

15

Example 82

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-D-Ala-NHCH₂CH₃

The procedure described in Example 10 was used but substituting Fmoc-D-Ala-Sieber ethylamide resin for Fmoc-Pro-Sieber amide resin. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-D-Ala-NHCH₂CH₃ as the trifluoroacetate salt: R_t = 2.95 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 968 (M+H)⁺.

25

Example 83

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Pip-NHCH₂CH₃

The procedure described in Example 10 was used but substituting Fmoc-Pip-Sieber ethylamide resin for Fmoc-Pro-Sieber amide resin. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Pip-NHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.30 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1008 (M+H)⁺.

Example 84

N-Ac-Sar-Gly-Val-D-Tyr(Et)-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-D-Tyr(Et)

5 for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-
10 Val-D-Tyr(Et)-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 6.01 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (APCI) m/e 1072 (M)⁺.

Example 85

N-Ac-Sar-Gly-Val-D-Cys(tBu)-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

15 The procedure described in Example 1 was used but substituting Fmoc-D-Cys(tBu) for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-
20 Val-D-Cys(tBu)-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 5.96 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (APCI) m/e 1040 (M)⁺.

Example 86

N-Ac-Sar-Gly-Val-D-Cys(Acm)-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

25 The procedure described in Example 1 was used but substituting Fmoc-D-Cys(Acm) for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-
30 Val-D-Cys(Acm)-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 5.12 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (APCI) m/e 1044 (M)⁺.

Example 87

N-Ac-Sar-Gly-Val-D-Tyr(Bzl)-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-D-Tyr(Bzl) for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-
5 water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Tyr(Bzl)-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 6.74 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (APCI) m/e 1135 (M+H)⁺.

10 Example 88

N-Ac-Sar-Gly-Val-D-Ser(Bzl)-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-D-Ser(Bzl) for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-
15 water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ser(Bzl)-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 5.95 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (APCI) m/e 1058 (M)⁺.

20 Example 89

N-Ac-Sar-Gly-Val-D-1Nal-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-D-1Nal for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting
25 groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-
water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-1Nal-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 6.30 min
(gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period);
30 MS (APCI) m/e 1081 (M+3)⁺.

Example 90

N-Ac-Sar-Gly-Val-D-tButylgly-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-D-tButylgly for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting
35 groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column

chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-tButylgly-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 5.46 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (APCI) m/e 994 (M)⁺.

Example 91

N-Ac-Sar-Gly-Val-D-Orn-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-D-Orn(Boc) for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Orn-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 1.69 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (APCI) m/e 995 (M)⁺.

Example 92

N-Ac-Sar-Gly-Val-D-Thr(Bzl)-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-D-Thr(Bzl) for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Thr(Bzl)-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 6.10 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (APCI) m/e 1072 (M)⁺.

Example 93

N-Ac-Sar-Gly-Val-D-2Nal-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-D-2Nal for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-2Nal-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 6.33 min

(gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (APCI) m/e 1078 (M^+).

Example 94

N-Ac-Sar-Gly-Val-D-Phe(4-Me)-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-D-Phe(4-Me) for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Phe(4-Me)-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.654 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1042 (M)⁺.

Example 95

N-Ac-Sar-Gly-Val-D-Phe(3,4-diMeO)-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-D-Phe(3,4-diMeO) for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Phe(3,4-diMeO)-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.006 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1088 (M)⁺.

Example 96

N-Ac-Sar-Gly-Val-D-Phe(3,4,5-triF)-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-D-Phe(3,4,5-triF) for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Phe(3,4,5-triF)-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.848 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1082 (M)⁺.

Example 97

N-Ac-Sar-Gly-Val-D-Phe(4-NO₂)-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-D-Phe(4-NO₂) for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Phe(4-NO₂)-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.483 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1073 (M)⁺.

Example 98

N-Ac-Sar-Gly-Val-D-Pen-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-D-Pen(Trt) for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Pen-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 2.928 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1012 (M)⁺.

Example 99

N-Ac-Sar-Gly-Val-D-Pen(Acm)-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-D-Pen(Acm) for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Pen(Acm)-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 2.415 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1083 (M)⁺.

Example 100

N-Ac-Sar-Gly-Val-D-Pen(Bzl)-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-D-Pen(Bzl) for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-
5 water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Pen(Bzl)-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 4.124 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1102 (M)⁺.

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Example 101

N-Ac-Sar-Gly-Val-D-Abu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-D-Abu for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Abu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 2.533 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 966 (M)⁺.
15
20

Example 102

N-Ac-Sar-Gly-Val-D-Phe(4-NH₂)-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-D-Phe(4-Boc-NH₂) for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Phe(4-NH₂)-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 2.545 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1043 (M)⁺.
25
30

Example 103

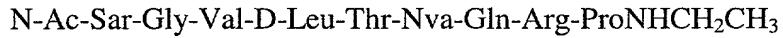
N-Ac-Sar-Gly-Val-D-Leu-Thr-Nva-Ala-Arg-ProNHCH₂CH₃

The procedure described in Example 15 was used but substituting Fmoc-Ala for Fmoc-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column
35

chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Leu-Thr-Nva-Ala-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 2.675 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period);

5 MS (ESI) m/e 952 (M)⁺.

Example 104



The procedure described in Example 15 was used but substituting Fmoc-Gln(Trt) for Fmoc-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Leu-Thr-Nva-Gln-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 2.46 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period);

15 MS (ESI) m/e 1009 (M)⁺.

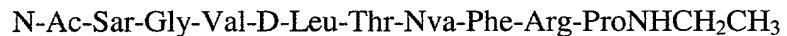
Example 105



The procedure described in Example 15 was used but substituting Fmoc-Met for Fmoc-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Leu-Thr-Nva-Met-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.219 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period);

25 MS (ESI) m/e 1012 (M)⁺.

Example 106



The procedure described in Example 15 was used but substituting Fmoc-Phe for Fmoc-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Leu-Thr-Nva-Phe-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.579 min

(gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period);
MS (ESI) m/e 1028 (M)⁺.

Example 107

5 N-Ac-Sar-Gly-Val-D-Leu-Thr-Nva-Pro-Arg-ProNHCH₂CH₃

The procedure described in Example 15 was used but substituting Fmoc-Pro for Fmoc-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-10 Val-D-Leu-Thr-Nva-Pro-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 2.704 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 978 (M)⁺.

15 Example 108

N-Ac-Sar-Gly-Val-D-Leu-Thr-Nva-Ser-Arg-ProNHCH₂CH₃

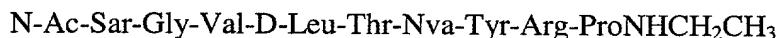
The procedure described in Example 15 was used but substituting Fmoc-Ser(tBu) for Fmoc-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-20 Val-D-Leu-Thr-Nva-Ser-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 2.510 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 968 (M)⁺.

25 Example 109

N-Ac-Sar-Gly-Val-D-Leu-Thr-Nva-Trp-Arg-ProNHCH₂CH₃

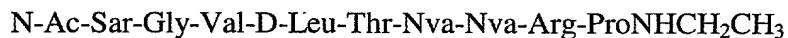
The procedure described in Example 15 was used but substituting Fmoc-Trp(Boc) for Fmoc-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-30 Val-D-Leu-Thr-Nva-Trp-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.625 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1067 (M)⁺.

Example 110



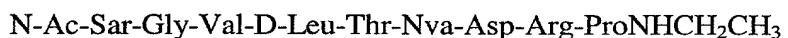
The procedure described in Example 15 was used but substituting Fmoc-Tyr(tBu) for Fmoc-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Leu-Thr-Nva-Tyr-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.017 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1044 (M)⁺.

Example 111



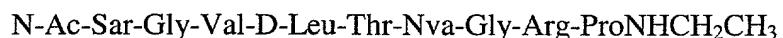
The procedure described in Example 15 was used but substituting Fmoc-Nva for Fmoc-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Leu-Thr-Nva-Nva-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.139 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 980 (M)⁺.

Example 112



The procedure described in Example 15 was used but substituting Fmoc-Asp(OtBu)-OH for Fmoc-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Leu-Thr-Nva-Asp-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 2.082 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 996 (M)⁺.

Example 113



The procedure described in Example 15 was used but substituting Fmoc-Gly for Fmoc-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-
5 water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Leu-Thr-Nva-Gly-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 2.623 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 938 (M)⁺.

10

Example 114

N-Ac-Sar-Gly-Val-D-Leu-Thr-Nva-Lys(Ac)-Arg-ProNHCH₂CH₃

The procedure described in Example 15 was used but substituting Fmoc-Lys(Ac) for Fmoc-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-
15 water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Leu-Thr-Nva-Lys(Ac)-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 2.599 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1051 (M)⁺.

20

Example 115

N-Ac-Sar-Gly-Val-D-Leu-Thr-Nva-Leu-Arg-ProNHCH₂CH₃

The procedure described in Example 15 was used but substituting Fmoc-Leu for Fmoc-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-
25 water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Leu-Thr-Nva-Leu-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.403 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period);
30 MS (ESI) m/e 994 (M)⁺.

Example 116

N-Ac-Sar-Gly-Val-D-Leu-Thr-Nva-2Nal-Arg-ProNHCH₂CH₃

The procedure described in Example 15 was used but substituting Fmoc-2Nal for
35 Fmoc-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column

chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Leu-Thr-Nva-2Nal-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 4.198 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period);
5 MS (ESI) m/e 1078 (M)⁺.

Example 117

N-Ac-Sar-Gly-Val-D-Leu-Thr-Nva-1Nal-Arg-ProNHCH₂CH₃

The procedure described in Example 15 was used but substituting Fmoc-1Nal for
10 Fmoc-Ile. After cleavage of the peptide from the resin and removal of the protecting
groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column
chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-
water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-
Val-D-Leu-Thr-Nva-1Nal-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 4.217 min
15 (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period);
MS (ESI) m/e 1078 (M)⁺.

Example 118

N-Ac-Sar-Gly-Val-D-Leu-Thr-Nva-Allylgly-Arg-ProNHCH₂CH₃

The procedure described in Example 15 was used but substituting Fmoc-Allylgly
20 for Fmoc-Ile. After cleavage of the peptide from the resin and removal of the protecting
groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column
chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-
water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-
25 Val-D-Leu-Thr-Nva-Allylgly-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 2.993
min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min
period); MS (ESI) m/e 978 (M)⁺.

Example 119

N-Ac-Sar-Gly-Val-D-Leu-Thr-Nva-Cit-Arg-ProNHCH₂CH₃

The procedure described in Example 15 was used but substituting Fmoc-Cit for
Fmoc-Ile. After cleavage of the peptide from the resin and removal of the protecting
groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column
chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-
35 water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-
Val-D-Leu-Thr-Nva-Cit-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 2.408 min

(gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period);
MS (ESI) m/e 1038 (M)⁺.

Example 120

5 N-Ac-Sar-Gly-Val-D-Leu-Ala-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 15 was used but substituting Fmoc-Ala for
Fmoc-Thr(tBu). After cleavage of the peptide from the resin and removal of the protecting
groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column
chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-
water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-
Val-D-Leu-Ala-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.481 min
(gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period);
MS (ESI) m/e 964 (M)⁺.

15 Example 121

N-Ac-Sar-Gly-Val-D-Leu-Pro-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 15 was used but substituting Fmoc-Pro for
Fmoc-Thr(tBu). After cleavage of the peptide from the resin and removal of the protecting
groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column
chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-
water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-
Val-D-Leu-Pro-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.621 min
(gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period);
MS (ESI) m/e 990 (M)⁺.

25 Example 122

N-Ac-Sar-Gly-Val-D-Leu-Trp-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 15 was used but substituting Fmoc-Trp(Boc)
for Fmoc-Thr(tBu). After cleavage of the peptide from the resin and removal of the
protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18
column chromatography using a solvent mixture varying in a gradient of 10% to 50%
acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-
Ac-Sar-Gly-Val-D-Leu-Trp-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t =
4.378 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30
min period); MS (ESI) m/e 1079 (M)⁺.

Example 123

N-Ac-Sar-Gly-Val-D-Leu-Tyr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 15 was used but substituting Fmoc-Tyr(tBu) for Fmoc-Thr(tBu). After cleavage of the peptide from the resin and removal of the
5 protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Leu-Tyr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.606 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30
10 min period); MS (ESI) m/e 1056 (M)⁺.

Example 124

N-Ac-Sar-Gly-Val-D-Leu-Nva-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 15 was used but substituting Fmoc-Nva for
15 Fmoc-Thr(tBu). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Leu-Nva-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.870 min
20 (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 992 (M)⁺.

Example 125

N-Ac-Sar-Gly-Val-D-Leu-Gly-Nva-Ile-Arg-ProNHCH₂CH₃

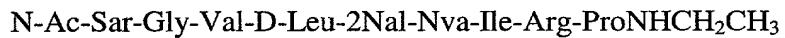
25 The procedure described in Example 15 was used but substituting Fmoc-Gly for Fmoc-Thr(tBu). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-
30 Val-D-Leu-Gly-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.397 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 950 (M)⁺.

Example 126

35 N-Ac-Sar-Gly-Val-D-Leu-Lys(Ac)-Nva-Ile-Arg-ProNHCH₂CH₃

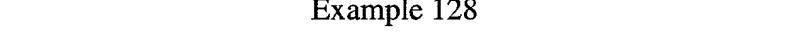
The procedure described in Example 15 was used but substituting Fmoc-Lys(Ac) for Fmoc-Thr(tBu). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Leu-Lys(Ac)-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt:
 5 $R_t = 3.365$ min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1063 (M)⁺.

10 Example 127



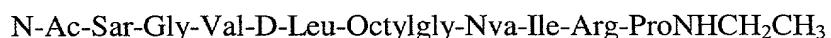
The procedure described in Example 15 was used but substituting Fmoc-2Nal for Fmoc-Thr(tBu). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Leu-2Nal-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 4.992 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1090 (M)⁺.

20



The procedure described in Example 15 was used but substituting Fmoc-1Nal for Fmoc-Thr(tBu). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Leu-1Nal-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 5.032 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1090 (M)⁺.

Example 129



The procedure described in Example 15 was used but substituting Fmoc-Octylgly for Fmoc-Thr(tBu). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18

column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Leu-Octylgly-Nva-Ile-Arg-ProNH₂CH₃ as the trifluoroacetate salt: R_t = 5.90 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 5 30 min period); MS (ESI) m/e 1062 (M)⁺.

Example 130

N-Ac-Sar-Gly-Val-D-Leu-Gln-Nva-Ile-Arg-ProNH₂CH₃

The procedure described in Example 15 was used but substituting Fmoc-Gln(Trt) 10 for Fmoc-Thr(tBu). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Leu-Gln-Nva-Ile-Arg-ProNH₂CH₃ as the trifluoroacetate salt: R_t = 15 3.323 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1021 (M)⁺.

Example 131

N-Ac-Sar-Gly-Val-D-Leu-Met-Nva-Ile-Arg-ProNH₂CH₃

The procedure described in Example 15 was used but substituting Fmoc-Met for 20 Fmoc-Thr(tBu). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly- 25 Val-D-Leu-Met-Nva-Ile-Arg-ProNH₂CH₃ as the trifluoroacetate salt: R_t = 3.901 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1024 (M)⁺.

Example 132

N-Ac-Sar-Gly-Val-D-Leu-Ser-Nva-Ile-Arg-ProNH₂CH₃

The procedure described in Example 15 was used but substituting Fmoc-Ser(tBu) 30 for Fmoc-Thr(tBu). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Leu-Ser-Nva-Ile-Arg-ProNH₂CH₃ as the trifluoroacetate salt: R_t = 35

3.414 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 980 (M)⁺.

Example 133

5 N-Ac-Sar-Gly-Val-D-Leu-Allylgly-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 15 was used but substituting Fmoc-Allylgly for Fmoc-Thr(tBu). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Leu-Allylgly-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.801 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 990 (M)⁺.

15 Example 134

N-Ac-Sar-Gly-Val-D-Leu-Ile-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 15 was used but substituting Fmoc-Ile for Fmoc-Thr(tBu). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Leu-Ile-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 4.028 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1006 (M)⁺.

25 Example 135

N-Ac-Sar-Gly-Val-D-Leu-D-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 15 was used but substituting Fmoc-D-Thr(tBu) for Fmoc-Thr(tBu). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Leu-D-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.437 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 994 (M)⁺.

Example 136

N-Ac-Sar-Gly-Val-D-Ile-Thr-Ile-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-Ile for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Ile-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.54 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period);
MS (ESI) m/e 1008 (M)⁺; Amino Acid Anal.: 1.07 Sar; 0.94 Gly; 0.91 Val; 3.02 Ile; 0.47 Thr; 1.24 Arg; 1.04 Pro.

Example 137

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nle-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-Nle for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Nle-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.80 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period);
MS (ESI) m/e 1006 (M)⁺.

Example 138

N-Ac-Sar-Gly-Val-D-Ile-Thr-Cit-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-Cit for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Cit-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 2.83 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period);
MS (ESI) m/e 1052 (M)⁺; Acid Anal.: 1.05 Sar; 1.00 Gly; 1.00 Val; 2.13 Ile; 0.65 Thr; 1.11 Cit; 1.49 Arg; 1.10 Pro.

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Example 139

N-Ac-Sar-Gly-Val-D-Ile-Thr-Met(O₂)-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-Met(O₂) for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Met(O₂)-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 2.701 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1058 (M)⁺; Acid Anal.: 1.36 Sar; 0.94 Gly; 0.62 Val; 2.06 Ile; 0.13 Thr; 0.66 Met(O₂); 1.50 Arg; 0.68 Pro.

Example 140

N-Ac-Sar-Gly-Val-D-Ile-Thr-Arg-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-Arg(Pmc) for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Arg-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 0.54 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1049 (M)⁺; Acid Anal.: 0.92 Sar; 0.74 Gly; 0.86 Val; 2.00 Ile; 0.49 Thr; 2.67 Arg; 1.00 Pro.

Example 141

N-Ac-Sar-Gly-Val-D-Ile-Thr-Tyr-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-Tyr(tBu) for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Tyr-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.048 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1058 (M)⁺; Acid Anal.: 0.88 Sar; 0.99 Gly; 0.97 Val; 1.97 Ile; 0.52 Thr; 0.92 Tyr; 1.58 Arg; 1.08 Pro.

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Example 142

N-Ac-Sar-Gly-Val-D-Ile-Thr-Glu-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-Glu(OtBu)-OH for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Glu-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 5 2.348 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1024 (M)⁺; Acid Anal.: 1.05 Sar; 1.024 Gly; 0.94 Val; 2.67 Ile; 10 0.47 Thr; 0.94 Glu; 2.20 Arg; 1.09 Pro.

Example 143

N-Ac-Sar-Gly-Val-D-Ile-Thr-Lys(Ac)-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-Lys(Ac) for 15 Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-20 Val-D-Ile-Thr-Lys(Ac)-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 2.744 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1065 (M)⁺; Acid Anal.: 1.03 Sar; 0.99 Gly; 0.95 Val; 2.04 Ile; 0.66 Thr; 1.05 Lys; 1.41 Arg; 1.02 Pro.

Example 144

N-Ac-Sar-Gly-Val-D-Ile-Thr-Propargylgly-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-35 Propargylgly for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Propargylgly-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.003 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 990 (M)⁺; Acid Anal.: 1.05 Sar; 1.00 Gly; 0.93 Val; 2.10 Ile; 0.54 Thr; 1.71 Arg; 0.97 Pro.

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Example 145

N-Ac-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-D-alloIle for Fmoc-D-Ile and Fmoc-Gln(Trt) for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 2.704 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1023 (M)⁺; Acid Anal.: 0.93 Sar; 0.94 Gly; 0.94 Val; 2.10 Ile; 0.51 Thr; 0.87 Glu; 1.45 Arg; 1.03 Pro.

Example 146

N-Ac-Sar-Gly-Val-D-Leu-Thr-Gln-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 15 was used but substituting Fmoc-Gln(Trt) for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Leu-Thr-Gln-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 2.685 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1023 (M)⁺; Acid Anal.: 0.98 Sar; 0.74 Gly; 0.95 Val; 1.04 Ile; 0.49 Thr; 1.04 Leu; 0.94 Glu; 1.63 Arg; 0.97 Pro.

Example 147

N-Ac-Bala-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 65 was used but substituting Fmoc-beta-alanine for Fmoc-4-amino-butrylic acid. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Bala-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 2.92 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1065 (M)⁺; Acid Anal.: 0.99 Sar; 0.99 Gly; 1.00 Val; 1.86 Ile; 0.49 Thr; 1.07 Nva; 1.51 Arg; 1.02 Pro.

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Example 148

N-Phenylacetyl-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 60 was used but substituting phenylacetic acid for butyric acid. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Phenylacetyl-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.83 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1070 (M)⁺; Acid Anal.: 1.04 Sar; 0.979 Gly; 1.01 Val; 1.90 Ile; 0.59 Thr; 1.09 Nva; 1.53 Arg; 1.03 Pro.

Example 149

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Pro-Azagly-NH₂

To a solution of N-Ac-Sar-Gly-Val-D-Ile-Thr(tBu)-Nva-Ile-Arg(Pmc)-Pro-OH (0.1288 g) in DMF was added semicarbazide hydrochloride (0.222 g) followed by DIEA (0.346 ml) and PyBrop (0.0513 g). The solution was stirred at rt for 36 hr. The solvent was removed in vacuo and the residue was treated with diethyl ether. The solid was filtered and then treated with (9:1) TFA/anisole (3 mL) at rt for 4 hr. The solvent was again removed in vacuo and the residue was treated with diethyl ether. The precipitate was filtered to give the crude product as a solid. This was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Pro-Azagly-NH₂ as the trifluoroacetate salt: R_t = 2.67 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1024 (M)⁺; Acid Anal.: 0.99 Sar; 0.98 Gly; 1.00 Val; 2.13 Ile; 0.56 Thr; 1.09 Nva; 0.92 Arg; 1.02 Pro.

Example 150

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Sar-NHCH₂CH₃

The procedure described in Example 76 was used but substituting Fmoc-Sar-Sieber ethylamide resin for Fmoc-D-Pro-Sieber ethylamide resin. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Sar-NHCH₂CH₃ as the trifluoroacetate salt: R_t = 2.93 min (gradient of 10% to 30% acetonitrile

in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 968 (M^+); Acid Anal.: 1.96 Sar; 0.96 Gly; 0.98 Val; 2.07 Ile; 0.55 Thr; 1.05 Nva; 1.49 Arg.

Example 151

5 N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Pro-SerNH₂

The procedure described in Example 75 was used but substituting Fmoc-Ser(tBu)-Sieber amide resin for Fmoc-D-Ala-Sieber amide resin. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Pro-SerNH₂ as the trifluoroacetate salt: R_t = 2.65 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1053 (M^+); Acid Anal.: 0.99 Sar; 0.95 Gly; 1.00 Val; 1.96 Ile; 0.57 Thr; 1.12 Nva; 1.03 Arg; 1.03 Pro; 0.27 Ser.

15

Example 152

N-Succinyl-Sar-Gly-Val-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 54 was used but substituting Fmoc-D-Leu for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Succinyl-Sar-Gly-Val-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 2.85 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1052 (M^+); Acid Anal.: 1.01 Sar; 0.93 Gly; 0.95 Val; 1.16 Leu; 1.10 Ile; 0.51 Thr; 1.04 Nva; 1.67 Arg; 0.96 Pro.

Example 153

N-Ac-Sar-Ala-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

30 The procedure described in Example 1 was used but substituting Fmoc-Ala for Fmoc-Gly. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Ala-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.056 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period);

MS (ESI) m/e 1008 (M)⁺; Acid Anal.: 1.32 Sar; 0.96 Ala; 0.94 Val; 2.10 Ile; 0.52 Thr; 0.98 Nva; 1.65 Arg; 1.01 Pro.

Example 154

5 N-Ac-Sar-Leu-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-Leu for Fmoc-Gly. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Leu-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.628 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1050 (M)⁺.

15 Example 155

N-Ac-Sar-Ser-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-Ser(tBu) for Fmoc-Gly. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Ser-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 2.955 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1024 (M)⁺.

25 Example 156

N-Ac-Sar-Phe-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-Phe for Fmoc-Gly. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Phe-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.83 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1084 (M)⁺.

Example 157

N-Ac-Sar-Glu-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-Glu(OtBu)-OH for Fmoc-Gly. After cleavage of the peptide from the resin and removal of the
5 protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Glu-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.08 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30
10 min period); MS (ESI) m/e 1065 (M)⁺.

Example 158

N-Ac-Sar-Pro-Val-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-Pro for
15 Fmoc-Gly and Fmoc-D-Leu for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Pro-Val-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.343 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1034 (M)⁺.
20

Example 159

N-Ac-Sar-Asn-Val-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

25 The procedure described in Example 1 was used but substituting Fmoc-Asn(Trt) for Fmoc-Gly and Fmoc-D-Leu for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Asn-Val-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.112 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1051 (M)⁺.
30

Example 160

N-Ac-Sar-Asp-Val-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-Asp(OtBu)-OH for Fmoc-Gly and Fmoc-D-Leu for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a 5 gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Asp-Val-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 2.9113 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1052 (M)⁺.

10

Example 161

N-Ac-Asn-Gly-Val-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-Asn(Trt) for Fmoc-Sar and Fmoc-D-Leu for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude 15 product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Asn-Gly-Val-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.06 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1037 (M)⁺.

20

Example 162

N-Ac-Gln-Gly-Val-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-Gln(Trt) for Fmoc-Sar and Fmoc-D-Leu for Fmoc-D-Ile. After cleavage of the peptide from the 25 resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Gln-Gly-Val-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.10 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1051 (M)⁺.

30

Example 163

N-Ac-Ser-Gly-Val-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-Ser(tBu) 35 for Fmoc-Sar and Fmoc-D-Leu for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude

product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Ser-Gly-Val-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.15 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1010 (M)⁺.

5
Example 164

N-Ac-Cit-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-Cit for Fmoc-Sar. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Cit-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 2.97 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1080 (M)⁺.

10
Example 165

N-Ac-Glu-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

15
The procedure described in Example 1 was used but substituting Fmoc-Glu(tBu)-OH for Fmoc-Sar. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-
20
Ac-Glu-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 2.69 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1052 (M)⁺.

25
Example 166

N-Ac-Gaba-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

30
The procedure described in Example 1 was used but substituting Fmoc-gamma-aminobutyric acid for Fmoc-Sar. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-
35
Ac-Gaba-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t =

3.17 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1008 (M^+).

Example 167

5 N-Ac-Bala-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-beta-alanine for Fmoc-Sar. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Bala-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.14 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 994 (M^+).

15 Example 168

N-Ac-Gln-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-Gln(Trt) for Fmoc-Sar. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Gln-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.00 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1051 (M^+).

25 Example 169

N-Ac-Sar-Gly-Gly-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-Gly for Fmoc-Val. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Gly-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 2.46 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 952 (M^+).

Example 170

N-Ac-Sar-Gly-Glu-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-Glu(OtBu)-OH for Fmoc-Val. After cleavage of the peptide from the resin and removal of the
5 protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Glu-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 1.74 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30
10 min period); MS (ESI) m/e 1024 (M)⁺.

Example 171

N-Ac-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNHCH(CH₃)₂

The procedure described in Example 4 was used but substituting Fmoc-Gln(Trt)
15 for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNHCH(CH₃)₂ as the trifluoroacetate salt: R_t = 2.80 min
20 (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1037 (M)⁺; Acid Anal.: 0.98 Sar; 0.94 Gly; 0.97 Val; 2.23 Ile; 0.51 Thr; 0.90 Glu; 1.16 Arg; 1.03 Pro.

Example 172

N-Ac-Sar-Gly-Val-D-Leu-Thr-Gln-Ile-Arg-ProNHCH(CH₃)₂

The procedure described in Example 4 was used but substituting Fmoc-D-Leu for
Fmoc-D-Ile and Fmoc-Gln(Trt) for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Leu-Thr-Gln-Ile-Arg-ProNHCH(CH₃)₂ as the trifluoroacetate salt: R_t = 2.90 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1037 (M)⁺; Acid Anal.: 1.05 Sar; 0.97 Gly; 0.99 Val; 1.30 Leu 1.11 Ile; 0.52 Thr; 0.89 Glu; 1.20 Arg; 1.04 Pro.
35

Example 173

H-Sar-Gly-Val-D-Leu-Thr-Gln-Ile-Arg-ProNHCH(CH₃)₂

The procedure described in Example 172 was used but omitting the last coupling with acetic acid. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield H-Sar-Gly-Val-D-Leu-Thr-Gln-Ile-Arg-ProNHCH(CH₃)₂ as the trifluoroacetate salt: R_t = 2.55 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 981 (M)⁺; Acid Anal.: 1.02 Sar; 0.93 Gly; 1.02 Val; 1.05 Leu; 1.02 Ile; 0.55 Thr; 0.84 Gln; 1.31 Arg; 1.03 Pro.

Example 174

N-Succinyl-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 54 was used but substituting Fmoc-Gln(Trt) for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Succinyl-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 2.02 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1081 (M)⁺; Acid Anal.: 1.00 Sar; 0.94 Gly; 1.00 Val; 2.00 Ile; 0.52 Thr; 0.87 Gln; 1.37 Arg; 1.05 Pro.

Example 175

N-Succinyl-Sar-Gly-Val-D-Leu-Thr-Gln-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 174 was used but substituting Fmoc-D-Leu for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Succinyl-Sar-Gly-Val-D-Leu-Thr-Gln-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 2.284 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1081 (M)⁺.

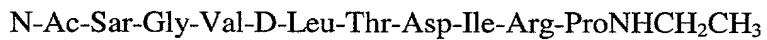
35

Example 176

N-Succinyl-Sar-Gly-Val-D-Leu-Thr-Gln-Ile-Arg-ProNHCH(CH₃)₂

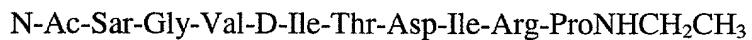
The procedure described in Example 4 was used but substituting Fmoc-D-Leu for Fmoc-D-Ile and Fmoc-Gln(Trt) for Fmoc-Nva. Following the coupling with Fmoc-Sar and protection the resin was treated with succinic anhydride/pyridine as described in Example 54. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Succinyl-Sar-Gly-Val-D-Leu-Thr-Gln-Ile-Arg-ProNHCH(CH₃)₂ as the trifluoroacetate salt: R_t = 2.56 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1095 (M)⁺; Acid Anal.: 0.95 Sar; 0.94 Gly; 1.02 Val; 1.02 Leu; 1.05 Ile; 0.56 Thr; 0.86 Gln; 1.00 Arg; 1.07 Pro.

Example 177



The procedure described in Example 146 was used but substituting Fmoc-Asp(OtBu)-OH for Fmoc-Gln(Trt). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Leu-Thr-Asp-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 2.53 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1010 (M)⁺; Acid Anal.: 1.00 Sar; 0.95 Gly; 1.01 Val; 1.02 Leu; 1.00 Ile; 0.56 Thr; 0.99 Asp; 1.43 Arg; 1.03 Pro.

Example 178



The procedure described in Example 142 was used but substituting Fmoc-Asp(OtBu)-OH for Fmoc-Glu(OtBu)-OH. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Asp-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 2.455 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1010 (M)⁺.

35

Example 179

N-Ac-Sar-Gly-Val-D-Ile-Thr-Asn-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 43 was used but substituting Fmoc-Asn(Trt) for Fmoc-Gln(Trt). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Asn-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 2.68 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1009 (M)⁺.

10

Example 180

N-Ac-Sar-Gly-Val-D-Ile-Thr-Met(O)-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 139 was used but substituting Fmoc-Met(O) for Fmoc-Met(O₂). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Met(O)-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 2.713 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1042 (M)⁺.

Example 181

N-Ac-Sar-Gly-Val-D-Leu-Thr-Asn-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 146 was used but substituting Fmoc-Asn(Trt) for Fmoc-Gln(Trt). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Leu-Thr-Asn-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 2.752 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1009 (M)⁺.

Example 182

The procedure described in Example 1 is used but separately substituting in the syntheses Fmoc-D-Ile with the following amino acids: Fmoc-D-Thr(tBu), Fmoc-D-Ser(tBu), Fmoc-D-Hser(tBu), Fmoc-D-Gln(Trt), Fmoc-D-Asn(Trt), Fmoc-D-Cit, Fmoc-D-

Hcit, Fmoc-D-Hle, Fmoc-D-Neopentylgly. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized
5 to yield the trifluoroacetate salt of the following peptides:

N-Ac-Sar-Gly-Val-D-Thr-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ser-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Hser-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Gln-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
10 N-Ac-Sar-Gly-Val-D-Asn-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Cit-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Hcit-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Hle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃, and
N-Ac-Sar-Gly-Val-D-Neopentylgly-Thr-Nva-Ile-Arg-ProNHCH₂CH₃.
15

Example 183

N-Ac-Sar-Gly-Val-D-Ile-Thr-Phe(4-CONH₂)-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 43 is used but substituting Fmoc-Phe[4-

20 CONH(Trt)] for Fmoc-Gln(Trt). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Phe(4-CONH₂)-Ile-Arg-ProNHCH₂CH₃.

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Example 184

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-His-ProNHCH₂CH₃

The procedure described in Example 1 is used but substituting Fmoc-His(Boc) for Fmoc-Arg(Pmc). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-His-ProNHCH₂CH₃.
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Example 185

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Lys(Isp)-ProNHCH₂CH₃

The procedure described in Example 1 is used but substituting Fmoc-Lys(N-epsilon-Isp,N-epsilon-Boc) for Fmoc-Arg(Pmc). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Lys(Isp)-ProNHCH₂CH₃.

Example 186

The procedure described in Example 185 is used but separately substituting in each synthesis Fmoc-Lys(N-epsilon-nicotinyl), Fmoc-Orn(N-delta-nicotinyl), Fmoc-Orn-(N-delta-Isp,N-epsilon-Boc), Fmoc-Phe(4-N-Isp,4-N-Boc), Fmoc-Cha-(4-N-Isp,4-N-Boc) instead of Fmoc-Lys(N-epsilon-Isp,N-epsilon-Boc). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude products are purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield the following peptides:

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Lys(Nic)-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Orn(Nic)-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Orn(Isp)-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Phe(4-NIsp)-ProNHCH₂CH₃, and
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Cha(4-NIsp)-ProNHCH₂CH₃.

Example 187

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Harg-ProNHCH₂CH₃

The procedure described in Example 1 is used but substituting Fmoc-Harg(Pmc) for Fmoc-Arg(Pmc). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Harg-ProNHCH₂CH₃.

Example 188

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Norarg-ProNHCH₂CH₃

The procedure described in Example 1 is used but substituting Fmoc-Norarg(N,N-bis-Boc) for Fmoc-Arg(Pmc). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18

column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Norarg-ProNHCH₂CH₃.

5

Example 189

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Cit-ProNHCH₂CH₃

The procedure described in Example 1 is used but substituting Fmoc-Cit for Fmoc-Arg(Pmc). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Cit-ProNHCH₂CH₃.

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Val-D-Ile-Thr-Nva-Ile-Cit-ProNHCH₂CH₃.

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Example 190

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Lys-ProNHCH₂CH₃

The procedure described in Example 1 is used but substituting Fmoc-Lys(Boc) for Fmoc-Arg(Pmc). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Lys-ProNHCH₂CH₃.

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Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Lys-ProNHCH₂CH₃.

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Example 191

N-Ac-Sar-Gly-Val-D-Ile-Phe(4-CH₂OH)-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 is used but substituting Fmoc-Phe[4-CH₂O(Trt)] for Fmoc-Thr(Trt). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Phe(4-CH₂OH)-Nva-Ile-Arg-ProNHCH₂CH₃.

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Ac-Sar-Gly-Val-D-Ile-Phe(4-CH₂OH)-Nva-Ile-Arg-ProNHCH₂CH₃.

35

Example 192

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Phe(4-guanidino)-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-Phe(4-bis-Boc-guanidino) for Fmoc-Arg(Pmc). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was

purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Phe(4-guanidino)-ProNHCH₂CH₃ as the trifluoroacetate salt: $R_t = 3.423$ min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1042 (M+H)⁺.

Example 193

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Aminopyrimidinylbutanoyl-ProNHCH₂CH₃.

The procedure described in Example 1 was used but substituting Fmoc-2-amino-4-[(2-amino)-pyrimidinyl]butanoic acid for Fmoc-Arg(Pmc). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Aminopyrimidinylbutanoyl-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.303 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1016 (M+H)⁺.

Example 194

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Phe(4-CH₂NHisp)-ProNHCH₂CH₃

The procedure described in Example 1 is used but substituting Fmoc-Phe (4-CH₂NHisp-Boc) for Fmoc-Arg(Pmc). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Phe(4-CH₂NHisp)-ProNHCH₂CH₃ as the trifluoroacetate salt.

Example 195

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Gly[4-Pip(N-amidino)]-ProNHCH₂CH₃

The procedure described in Example 1 is used but substituting Fmoc-Gly-4-piperidinyl[N-amidino(BOC)₂] for Fmoc-Arg(Pmc). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Gly

(4-Pip-amidino)-ProNHCH₂CH₃ as the trifluoroacetate salt.

Example 196

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Ala[4-Pip(N-amidino)]-ProNHCH₂CH₃

5 The procedure described in Example 1 is used but substituting Fmoc-Ala-[4-piperidinyl-(N',N"-bis-Boc-amidino)] for Fmoc-Arg(Pmc). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions
10 are lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Ala[4-Pip(N-amidino)]-Pro-NHCH₂CH₃ as the trifluoroacetate salt.

Example 197

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Ala(3-guanidino)-ProNHCH₂CH₃

15 The procedure described in Example 1 is used but substituting Fmoc-Ala-[3-(bis-Boc)guanidino] for Fmoc-Arg(Pmc). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized
20 to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Ala(3-guanidino)-ProNHCH₂CH₃ as the trifluoroacetate salt.

Example 198

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Ala(3-pyrrolidinylamidino)-ProNHCH₂CH₃

25 The procedure described in Example 1 is used but substituting Fmoc-Ala[3-pyrrolidinyl-(2-N,N'-bis-Boc-amidino)] for Fmoc-Arg(Pmc). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are
30 lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Ala-(3-pyrrolidinyl-amidino)-ProNHCH₂CH₃ as the trifluoroacetate salt.

Example 199

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Orn(2-imidazo)-ProNHCH₂CH₃

35 The procedure described in Example 1 is used but substituting Fmoc-Orn-[N-2-(1-Boc)imidazolinyl] for Fmoc-Arg(Pmc). After cleavage of the peptide from the resin and

removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Orn(2-imidazo)-ProNHCH₂CH₃ as the trifluoroacetate salt.

5

Example 200

N-Succinyl-Sar-Gly-Val-D-alloIle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 54 is used but substituting Fmoc-D-alloIle for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Succinyl-Sar-Gly-Val-D-alloIle-Thr-Nva Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt.

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Example 201

N-Succinyl-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 54 is used but substituting Fmoc-Gln(Trt) for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Succinyl-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt.

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Example 202

N-Succinyl-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-Pro-D-AlaNH₂

The procedure described in Example 75 is used but substituting Fmoc-Gln(Trt) for Fmoc-Nva and, after the coupling with Fmoc-Sar, acylating the peptide resin with succinic anhydride as described in Example 54. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Succinyl-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-Pro-D-AlaNH₂ as the trifluoroacetate salt.

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Example 203

N-Succinyl-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 201 is used but substituting Fmoc-D-alloIle for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Succinyl-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt.

Example 204

N-Succinyl-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-Pro-D-AlaNH₂

The procedure described in Example 202 is used but substituting Fmoc-D-alloIle for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Succinyl-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-Pro-D-AlaNH₂ as the trifluoroacetate salt.

Example 205

N-Succinyl-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH(CH₃)₂

The procedure described in Example 175 is used but substituting Fmoc-D-alloIle for Fmoc-D-Leu. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Succinyl-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH(CH₃)₂ as the trifluoroacetate salt.

Example 206

N-Succinyl-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNHCH(CH₃)₂

The procedure described in Example 205 is used but substituting Fmoc-D-Ile for Fmoc-D-alloIle. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Succinyl-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNHCH(CH₃)₂ as the trifluoroacetate salt.

Example 207

N-Ac-Sar-Gly-Val-D-alloIle-Thr-Nva-Ile-Arg-Pro-D-AlaNH₂

The procedure described in Example 75 is used but substituting Fmoc-D-alloIle for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting

5 groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-
Val-D-alloIle-Thr-Nva-Ile-Arg-Pro-D-Ala-NH₂ as the trifluoroacetate salt.

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Example 208

N-Ac-Sar-Gly-Val-D-alloIle-Thr-Nva-Ile-Arg-ProNHCH(CH₃)₂

The procedure described in Example 4 is used but substituting Fmoc-D-alloIle for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting

15 groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-
Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH(CH₃)₂ as the trifluoroacetate salt.

20

Example 209

N-Ac-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-Pro-D-AlaNH₂

The procedure described in Example 75 is used but substituting Fmoc-Gln(Trt) for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting

25 groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-
Val-D-Ile-Thr-Gln-Ile-Arg-Pro-D-AlaNH₂ as the trifluoroacetate salt.

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Example 210

N-Ac-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNHCH(CH₃)₂

The procedure described in Example 4 is used but substituting Fmoc-Gln(Trt) for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting

35 groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-
Val-D-Ile-Thr-Gln-Ile-Arg-ProNHCH(CH₃)₂ as the trifluoroacetate salt.

Example 211

N-Ac-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-Pro-D-AlaNH₂

The procedure described in Example 209 is used but substituting Fmoc-D-alloIle for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-Pro-D-AlaNH₂ as the trifluoroacetate salt.

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Example 212

N-Ac-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH(CH₃)₂

The procedure described in Example 210 is used but substituting Fmoc-D-alloIle for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH(CH₃)₂ as the trifluoroacetate salt.

20

Example 213

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Pro-SarNH₂

The procedure described in Example 75 is used but substituting Fmoc-Sar-Seiberamide-resin for Fmoc-D-Ala-Seiberamide-resin. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Pro-SarNH₂ as the trifluoroacetate salt.

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Example 214

N-Ac-Sar-Gly-Val-D-alloIle-Thr-Nva-Ile-Arg-Pro-SarNH₂

The procedure described in Example 213 is used but substituting Fmoc-D-alloIle for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-alloIle-Thr-Nva-Ile-Arg-Pro-SarNH₂ as the trifluoroacetate salt.

Example 215

N-Ac-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-Pro-SarNH₂

The procedure described in Example 213 is used but substituting Fmoc-Gln(Trt) for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-Pro-SarNH₂ as the trifluoroacetate salt.

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Example 216

N-Ac-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-Pro-SarNH₂

The procedure described in Example 215 is used but substituting Fmoc-D-alloIle for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-Pro-SarNH₂ as the trifluoroacetate salt.

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Example 217

N-Ac-Sar-Gly-Val-D-alloIle-Thr-Ser-Ile-Arg-Pro-D-AlaNH₂

The procedure described in Example 207 is used but substituting Fmoc-Ser(tBu) for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-alloIle-Thr-Ser-Ile-Arg-Pro-D-AlaNH₂ as the trifluoroacetate salt.

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Example 218

N-Ac-Sar-Gly-Val-D-alloIle-Thr-Ser-Ile-Arg-ProNHCH(CH₃)₂

The procedure described in Example 208 is used but substituting Fmoc-Ser(tBu) for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-alloIle-Thr-Ser-Ile-Arg-ProNHCH(CH₃)₂ as the trifluoroacetate salt.

Example 219

N-Ac-Sar-Gly-Val-D-alloIle-Thr-Ser-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 15 is used but substituting Fmoc-Ser(tBu) for

5 Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-alloIle-Thr-Ser-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt.

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Example 220

N-Ac-Sar-Gly-Val-D-Ile-Thr-Orn(Ac)-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 is used but substituting Fmoc-Orn(Ac) for

15 Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Orn(Ac)-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt.

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Example 221

N-Ac-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-Pro-AzaglyNH₂

The procedure described in Example 149 is used but substituting Fmoc-Gln(Trt)

for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-Pro-AzaglyNH₂ as the trifluoroacetate salt.

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Example 222

N-Ac-Sar-Gly-Val-D-alloIle-Thr-Nva-Ile-Arg-Pro-AzaglyNH₂

The procedure described in Example 149 is used but substituting Fmoc-D-alloIle

for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-alloIle-Thr-Nva-Ile-Arg-Pro-AzaglyNH₂ as the trifluoroacetate salt.

Example 223

N-Ac-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-Pro-AzaglyNH₂

The procedure described in Example 222 is used but substituting Fmoc-Gln(Trt)

5 for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-Pro-AzaglyNH₂ as the trifluoroacetate salt.

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Example 224

N-(2-THFcarbonyl)-Sar-Gly-Val-D-alloIle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 61 is used but substituting tetrahydro-2-furoic acid for acetic acid. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-(2-THFcarbonyl)-Sar-Gly-Val-D-alloIle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt.

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Example 225

N-(2-THFcarbonyl)-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 61 is used but substituting Fmoc-Gln(Trt) for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-(2-THFcarbonyl)-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt.

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Example 226

N-(2-THFcarbonyl)-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 225 is used but substituting Fmoc-D-alloIle for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-

water containing 0.01% TFA. The pure fractions are lyophilized to yield N-(2-THFcarbonyl)-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt.

5

Example 227

N-(2-THFcarbonyl)-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-Pro-D-AlaNH₂

The procedure described in Example 209 is used but substituting tetrahydro-2-furoic acid for acetic acid. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-(2-THFcarbonyl)-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-Pro-D-AlaNH₂ as the trifluoroacetate salt.

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Example 228

N-(2-THFcarbonyl)-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-Pro-D-AlaNH₂

The procedure described in Example 227 is used but substituting Fmoc-D-alloIle for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-(2-THFcarbonyl)-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-Pro-D-AlaNH₂ as the trifluoroacetate salt.

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Example 229

N-(2-THFcarbonyl)-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH(CH₃)₂

The procedure described in Example 4 is used but substituting Fmoc-D-alloIle for Fmoc-D-Ile, Fmoc-Gln(Trt) for Fmoc-Nva and tetrahydro-2-furoic acid for acetic acid. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-(2-THFcarbonyl)-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH(CH₃)₂ as the trifluoroacetate salt.

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Example 230

The procedures described in Examples 224, 225, 226, 227, 228, and 229 are used but substituting N-acetyl-6-aminocaproic acid (6-Ac-Aca) instead of tetrahydro-2-furoyl. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography 5 using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield the following peptides as trifluoroacetate salt:

N-(6-Ac-Aca)-Sar-Gly-Val-D-alloIle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-(6-Ac-Aca)-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
10 N-(6-Ac-Aca)-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
N-(6-Ac-Aca)-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-Pro-D-AlaNH₂,
N-(6-Ac-Aca)-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-Pro-D-AlaNH₂, and
N-(6-Ac-Aca)-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH(CH₃)₂.

15 Example 231

The procedures described in Examples 224, 225, 226, 227, 228, and 229 are used but substituting N-acetyl-4-aminobutyric acid (4-Ac-Gaba) instead of N-acetyl-6-aminocaproic acid. After cleavage of the peptide from the resin and removal of the 20 protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield the following peptides as trifluoroacetate salt:

N-(4-Ac-Gaba)-Sar-Gly-Val-D-alloIle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-(4-Ac-Gaba)-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
25 N-(4-Ac-Gaba)-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
N-(4-Ac-Gaba)-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-Pro-D-AlaNH₂,
N-(4-Ac-Gaba)-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-Pro-D-AlaNH₂, and
N-(4-Ac-Gaba)-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH(CH₃)₂.

30 Example 232

The procedures described in Examples 224, 225, 226, 227, 228, and 229 are used but substituting 2-furoic acid instead of tetrahydro-2-furoic acid. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture 35 varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield the following peptides as trifluoroacetate salt:

N-(2-Furoyl)-Sar-Gly-Val-D-alloIle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-(2-Furoyl)-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
N-(2-Furoyl)-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
N-(2-Furoyl)-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-Pro-D-AlaNH₂,
5 N-(2-Furoyl)-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-Pro-D-AlaNH₂, and
N-(2-Furoyl)-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH(CH₃)₂.

Example 233

The procedures described in Examples 224, 225, 226, 227, 228, and 229 are used
10 but substituting shikimic acid instead of tetrahydro-2-furoic acid. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield the following peptides as trifluoroacetate salt:

15 N-(Shikimyl)-Sar-Gly-Val-D-alloIle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-(Shikimyl)-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
N-(Shikimyl)-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
N-(Shikimyl)-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-Pro-D-AlaNH₂,
N-(Shikimyl)-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-Pro-D-AlaNH₂, and
20 N-(Shikimyl)-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH(CH₃)₂.

Example 234

The procedures described in Examples 224, 225, 226, 227, 228, and 229 are used but substituting 2-methyl-nicotinic acid instead of tetrahydro-2-furoic acid. After cleavage 25 of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield the following peptides:

30 N-(2-Me-Nicotinyl)-Sar-Gly-Val-D-alloIle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-(2-Me-Nicotinyl)-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
N-(2-Me-Nicotinyl)-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
N-(2-Me-Nicotinyl)-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-Pro-D-AlaNH₂,
N-(2-Me-Nicotinyl)-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-Pro-D-AlaNH₂, and
35 N-(2-Me-Nicotinyl)-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH(CH₃)₂.

Example 235

N-Ac-Sar-Gly-Val-D-alloIle-Thr-Leu-Ile-Arg-Pro-D-AlaNH₂

The procedure described in Example 75 is used but substituting Fmoc-D-alloIle for Fmoc-D-Ile and Fmoc-Leu for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-alloIle-Thr-Leu-Ile-Arg-Pro-D-AlaNH₂ as the trifluoroacetate salt.

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Example 236

N-Ac-Sar-Gly-Val-D-Ile-Thr-Leu-Ile-Arg-ProNHCH(CH₃)₂

The procedure described in Example 4 is used but substituting Fmoc-Leu for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Leu-Ile-Arg-ProNHCH(CH₃)₂ as the trifluoroacetate salt.

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Example 237

N-Ac-Sar-Gly-Val-D-alloIle-Thr-Leu-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 73 is used but substituting Fmoc-D-alloIle for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-alloIle-Thr-Leu-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt.

30

Example 238

N-Ac-Sar-Gly-Val-D-Ile-Thr-Leu-Ile-Arg-Pro-D-AlaNH₂

The procedure described in Example 75 is used but substituting Fmoc-Leu for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Leu-Ile-Arg-Pro-D-AlaNH₂ as the trifluoroacetate salt.

Example 239

N-Succinyl-Sar-Gly-Val-D-Ile-Thr-Leu-Ile-Arg-Pro-D-AlaNH₂

The procedure described in Example 75 is used but substituting Fmoc-Leu for Fmoc-Nva and acylating with succinic anhydride after the coupling with Fmoc-Sar and deprotection as described in Example 54. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Succinyl-Sar-Gly-Val-D-Ile-Thr-Leu-Ile-Arg-Pro-D-AlaNH₂ as the trifluoroacetate salt.

Example 240

N-Succinyl-Sar-Gly-Val-D-Ile-Thr-Leu-Ile-Arg-ProNHCH(CH₃)₂

The procedure described in Example 206 is used but substituting Fmoc-Leu for Fmoc-Gln(Trt) and acylating with succinic anhydride after the coupling with Fmoc-Sar and deprotection as described in Example 54. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Succinyl-Sar-Gly-Val-D-Ile-Thr-Leu-Ile-Arg-ProNHCH(CH₃)₂ as the trifluoroacetate salt.

Example 241

The procedures described in Examples 201, 202 and 203 are used but substituting

Fmoc-Leu instead of Fmoc-Gln(Trt). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield the following peptides:

30 N-Succinyl-Sar-Gly-Val-D-Ile-Thr-Leu-Ile-Arg-ProNHCH₂CH₃,
 N-Succinyl-Sar-Gly-Val-D-alloIle-Thr-Leu-Ile-Arg-ProNHCH₂CH₃, and
 N-Succinyl-Sar-Gly-Val-D-alloIle-Thr-Leu-Ile-Arg-Pro-D-AlaNH₂.

Example 242

35 N-Succinyl-Sar-Gly-Val-D-Ile-Thr-Leu-Ile-Arg-Pro-AzaglyNH₂

The procedure described in Example 149 is used but substituting Fmoc-Leu for Fmoc-Nva and acylating with succinic anhydride after the coupling with Fmoc-Sar and deprotection as described in Example 54. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Succinyl-Sar-Gly-Val-D-Ile-Thr-Leu-Ile-Arg-Pro-AzaglyNH₂ as the trifluoroacetate salt.

Example 243

N-Ac-Sar-Gly-Val-D-alloIle-Thr-Nva-Ile-Arg-ProNHethyl-(1-pyrrolidine)

The procedure described in Example 5 is used but substituting Fmoc-D-alloIle for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-alloIle-Thr-Nva-Ile-Arg-ProNHethyl-(1-pyrrolidine) as the trifluoroacetate salt.

Example 244

N-Ac-Sar-Gly-Val-D-alloIle-Thr-Nva-Ile-Arg-ProNH(ethyl-1-cyclohexyl)

The procedure described in Example 8 is used but substituting Fmoc-D-alloIle for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-alloIle-Thr-Nva-Ile-Arg-ProNH(ethyl-1-cyclohexyl) as the trifluoroacetate salt.

Example 245

N-Ac-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNHethyl-(1-pyrrolidine)

The procedure described in Example 5 is used but substituting Fmoc-Gln(Trt) for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNHethyl-(1-pyrrolidine) as the trifluoroacetate salt.

Example 246

N-Ac-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNH(ethyl-1-cyclohexyl)

The procedure described in Example 8 is used but substituting Fmoc-Gln(Trt) for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNH(ethyl-1-cyclohexyl) as the trifluoroacetate salt.

Example 247

N-Succinyl-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNH(ethyl-1-cyclohexyl)

The procedure described in Example 246 is used but acylating the peptide resin with succinic anhydride after the coupling with Fmoc-Sar and deprotection as described in Example 54. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Succinyl-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNH(ethyl-1-cyclohexyl) as the trifluoroacetate salt.

Example 248

The procedures described in Examples 11 is used but substituting the appropriate protected amino acids as described in Examples 14, 43, 74, 73, 54, 174, and 132 respectively. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield the following peptides as trifluoroacetate salt:

N-Ac-Sar-Gly-Val-D-alloIle-Thr-Nva-Ile-Arg-ProNHCH₂CH₂OCH₃,

N-Ac-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNHCH₂CH₂OCH₃,

30 N-Ac-Sar-Gly-Val-D-Ile-Thr-Ser-Ile-Arg-ProNH₂CH₂CH₂OCH₃,

N-Ac-Sar-Gly-Val-D-Ile-Thr-Leu-Ile-Arg-ProNHCH₂CH₂OCH₃,

N-Succinyl-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₂OCH₃,

N-Succinyl-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNHCH₂CH₂OCH₃,

N-Succinyl-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH₂CH₂OCH₃,

35 N-Ac-Sar-Gly-Val-D-Ile-Ser-Nva-Ile-Arg-ProNHCH₂CH₂OCH₃, and

N-Ac-Sar-Gly-Val-D-Leu-Ser-Nva-Ile-Arg-ProNHCH₂CH₂OCH₃.

Example 249

The procedures described in Examples 49 is used but substituting the appropriate protected amino acids as described in Examples 14, 4, 75, 54 and 132 respectively. After 5 cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield the following peptides as trifluoroacetate salt:

10 N-Ac-Sar-Gly-Val-D-alloIle-Thr-Allygly-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Allygly-Ile-Arg-ProNHCH(CH₃)₂,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Allygly-Ile-Arg-Pro-D-AlaNH₂,
N-Ac-Sar-Gly-Val-D-alloIle-Thr-Allygly-Ile-Arg-Pro-D-AlaNH₂,
N-Succinyl-Sar-Gly-Val-D-Ile-Thr-Allygly-Ile-Arg-Pro-D-AlaNH₂,
15 N-Ac-Sar-Gly-Val-D-Ile-Ser-Allygly-Ile-Arg-Pro-ProNHCH₂CH₃, and
N-Ac-Sar-Gly-Val-D-Leu-Ser-Allygly-Ile-Arg-Pro-ProNHCH₂CH₃.

Example 250

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Pro-D-SerNH₂

20 The procedure described in Example 75 is used but substituting Fmoc-D-Ser(tBu)-Sieber amide resin for Fmoc-D-Ala-Sieber amide resin. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions 25 are lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Pro-D-SerNH₂ as the trifluoroacetate salt.

Example 251

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHOH

30 The procedure described in Example 149 is used but hydroxylamine hydrochloride for semicarbazide hydrochloride. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-35 Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHOH as the trifluoroacetate salt.

Example 252

N-Ac-Sar-Gly-Val-D-Ile-Ser-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 132 is used but substituting Fmoc-D-Ile for Fmoc-D-Leu. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Ser-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt.

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Example 253

N-Ac-Sar-Gly-Val-D-alloIle-Ser-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 132 is used but substituting Fmoc-D-alloIle for Fmoc-D-Leu. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-alloIle-Ser-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt.

20

Example 254

N-Ac-Sar-Gly-Val-D-Leu-Hser-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 132 is used but substituting Fmoc-Hser(tBu) for Fmoc-Ser(tBu). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Leu-Hser-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt.

30

Example 255

N-Ac-Sar-Gly-Gln-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-Gln(Trt) for Fmoc-Val. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Gln-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 2.36 min

(gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period);
MS (ESI) m/e 1023 (M)⁺.

Example 256

5 N-Ac-Sar-Gly-Nva-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-Nva for Fmoc-Val. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Nva-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.28 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 994 (M)⁺.

15 Example 257

N-Ac-Sar-Gly-Ile-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-Ile for Fmoc-Val. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Ile-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.55 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1008 (M)⁺.

25 Example 258

N-Ac-Sar-Gly-Phe-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-Phe for Fmoc-Val. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Phe-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.77 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1042 (M)⁺.

Example 259

N-Ac-Sar-Gly-Leu-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-Leu for Fmoc-Val. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Leu-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.56 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period);
MS (ESI) m/e 1008 (M)⁺.

Example 260

N-Ac-Sar-Gly-Ser-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-Ser(tBu) for Fmoc-Val. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Ser-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 2.41 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 982 (M)⁺.

Example 261

N-Ac-Thr-Gly-Val-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 was used but substituting Fmoc-Thr(tBu) for Fmoc-Sar and Fmoc-D-Leu for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Thr-Gly-Val-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.33 min (gradient of 10% to 30% acetonitrile in water containing 0.01% TFA over 30 min period); MS (ESI) m/e 1024 (M)⁺.

Example 262

The procedures described in Example 46 is used but substituting the appropriate protected amino acids as describes in Examples 75, 4, 54, and 132. After cleavage of the

peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield the following peptides as trifluoroacetate salt:

5 N-Ac-Sar-Gly-Val-D-alloIle-Thr-Ala-Ile-Arg-ProNHCH₂CH₃,
 N-Ac-Sar-Gly-Val-D-Ile-Thr-Ala-Ile-Arg-ProNHCH(CH₃)₂,
 N-Ac-Sar-Gly-Val-D-Ile-Thr-Ala-Ile-Arg-Pro-D-AlaNH₂,
 N-Ac-Sar-Gly-Val-D-alloIle-Thr-Ala-Ile-Arg-Pro-D-AlaNH₂,
 N-Succinyl-Sar-Gly-Val-D-Ile-Thr-Ala-Ile-Arg-Pro-D-AlaNH₂,
10 N-Ac-Sar-Gly-Val-D-Ile-Ser-Ala-Ile-Arg-ProNHCH₂CH₃, and
 N-Ac-Sar-Gly-Val-D-Leu-Ser-Ala-Ile-Arg-ProNHCH₂CH₃.

Example 263

15 The procedures described in Example 262 is used but substituting Fmoc-Val for Fmoc-Ala. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield the following peptides as trifluoroacetate salt:

20 N-Ac-Sar-Gly-Val-D-alloIle-Thr-Val-Ile-Arg-ProNHCH₂CH₃,
 N-Ac-Sar-Gly-Val-D-Ile-Thr-Val-Ile-Arg-ProNHCH(CH₃)₂,
 N-Ac-Sar-Gly-Val-D-Ile-Thr-Val-Ile-Arg-Pro-D-AlaNH₂,
 N-Ac-Sar-Gly-Val-D-alloIle-Thr-Val-Ile-Arg-Pro-D-AlaNH₂,
25 N-Succinyl-Sar-Gly-Val-D-Ile-Thr-Val-Ile-Arg-Pro-D-AlaNH₂,
 N-Ac-Sar-Gly-Val-D-Ile-Ser-Val-Ile-Arg-ProNHCH₂CH₃, and
 N-Ac-Sar-Gly-Val-D-Leu-Ser-Val-Ile-Arg-ProNHCH₂CH₃.

Example 264

30 The procedures described in Example 263 is used but substituting Fmoc-DNva for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield the following peptides as trifluoroacetate salt:

35 N-Ac-Sar-Gly-Val-D-alloIle-Thr-D-Nva-Ile-Arg-ProNHCH₂CH₃,

N-Ac-Sar-Gly-Val-D-Ile-Thr-D-Nva-Ile-Arg-ProNHCH(CH₃)₂,
N-Ac-Sar-Gly-Val-D-Ile-Thr-D-Nva-Ile-Arg-Pro-D-AlaNH₂,
N-Ac-Sar-Gly-Val-D-alloIle-Thr-D-Nva-Ile-Arg-Pro-D-AlaNH₂,
N-Succinyl-Sar-Gly-Val-D-Ile-Thr-D-Nva-Ile-Arg-Pro-D-AlaNH₂,
5 N-Ac-Sar-Gly-Val-D-Ile-Ser-D-Nva-Ile-Arg-Pro-ProNHCH₂CH₃, and
N-Ac-Sar-Gly-Val-D-Leu-Ser-D-Nva-Ile-Arg-Pro-ProNHCH₂CH₃.

Example 265

N-Ac-Sar-Gly-Val-D-Ile-Ser-Gln-Ile-Arg-ProNHCH₂CH₃

10 The procedure described in Example 132 is used but substituting Fmoc-D-Ile for
Fmoc-D-Leu and Fmoc-Gln(Trt) for Fmoc-Nva. After cleavage of the peptide from the
resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude
product is purified by C-18 column chromatography using a solvent mixture varying in a
gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are
15 lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Ser-Gln-Ile-Arg-ProNHCH₂CH₃ as the
trifluoroacetate salt.

Example 266

N-Ac-Sar-Gly-Val-D-Leu-Ser-Gln-Ile-Arg-ProNHCH₂CH₃

20 The procedure described in Example 132 is used but substituting Fmoc-Gln(Trt)
for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting
groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column
chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-
water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-
25 Val-D-Leu-Ser-Gln-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt.

Example 267

N-Ac-Sar-Gly-Val-D-Leu-Ser-Nva-Ile-Arg-Pro-D-AlaNH₂

30 The procedure described in Example 75 is used but substituting Fmoc-D-Leu for
Fmoc-D-Ile and Fmoc-Ser(tBu) for Fmoc-Thr(tBu). After cleavage of the peptide from
the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude
product is purified by C-18 column chromatography using a solvent mixture varying in a
gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are
lyophilized to yield N-Ac-Sar-Gly-Val-D-Leu-Ser-Nva-Ile-Arg-Pro-D-AlaNH₂ as the
35 trifluoroacetate salt.

Example 268

N-Ac-Sar-Gly-Val-D-Ile-Ser-Nva-Ile-Arg-Pro-D-AlaNH₂

The procedure described in Example 267 is used but substituting Fmoc-D-Ile for Fmoc-D-Leu and Fmoc-Ser(tBu) for Fmoc-Thr(tBu). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Ser-Nva-Ile-Arg-Pro-D-AlaNH₂ as the trifluoroacetate salt.

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Example 269

N-Succinyl-Sar-Gly-Val-D-Leu-Ser-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 54 is used but substituting Fmoc-D-Leu for Fmoc-D-Ile and Fmoc-Ser(tBu) for Fmoc-Thr(tBu). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Succinyl-Sar-Gly-Val-D-Leu-Ser-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt.

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Example 270

N-Succinyl-Sar-Gly-Val-D-Ile-Ser-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 269 is used but substituting Fmoc-D-Ile for Fmoc-D-Leu. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Succinyl-Sar-Gly-Val-D-Ile-Ser-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt.

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Example 271

N-Succinyl-Sar-Gly-Val-D-Leu-Ser-Gln-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 270 is used but substituting Fmoc-D-Leu for Fmoc-D-Ile and Fmoc-Gln(Trt) for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are

lyophilized to yield N-Succinyl-Sar-Gly-Val-D-Leu-Ser-Gln-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt.

Example 272

N-Succinyl-Sar-Gly-Val-D-Ile-Ser-Gln-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 270 is used but substituting Fmoc-Gln(Trt) for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Succinyl-Sar-Gly-Val-D-Ile-Ser-Gln-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt.

Example 273

N-Ac-Sar-Gly-Val-D-Ile-Ser-Ser-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 265 is used but substituting Fmoc-Ser(tBu) for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Ser-Ser-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt.

Example 274

N-Ac-Sar-Gly-Val-D-Leu-Ser-Ser-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 266 is used but substituting Fmoc-Ser(tBu) for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Leu-Ser-Ser-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt.

Example 275

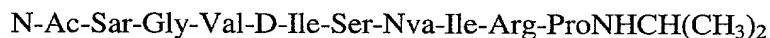
N-Ac-Sar-Gly-Val-D-Leu-Ser-Nva-Ile-Arg-ProNHCH(CH₃)₂

The procedure described in Example 13 is used but substituting Fmoc-D-Leu for Fmoc-D-Ile and Fmoc-Ser(tBu) for Fmoc-Thr(tBu). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a

gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Leu-Ser-Nva-Ile-Arg-ProNHCH(CH₃)₂ as the trifluoroacetate salt.

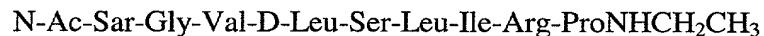
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Example 276



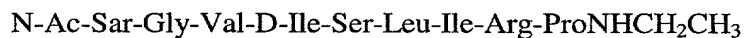
The procedure described in Example 13 is used but substituting Fmoc-Ser(tBu) for Fmoc-Thr(tBu). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Ser-Nva-Ile-Arg-ProNHCH(CH₃)₂ as the trifluoroacetate salt.

Example 277



The procedure described in Example 132 is used but substituting Fmoc-Leu for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Leu-Ser-Leu-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt.

Example 278



The procedure described in Example 277 is used but substituting Fmoc-D-Ile for Fmoc-D-Leu. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Ser-Leu-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt.

Example 279



The procedure described in Example 132 is used but substituting Fmoc-D-alloIle for Fmoc-D-Leu. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18

column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-alloIle-Ser-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt.

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Example 280

N-Ac-Sar-Gly-Val-D-alloIle-Ser-Gln-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 265 is used but substituting Fmoc-D-alloIle for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-alloIle-Ser-Gln-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt.

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Example 281

N-Succinyl-Sar-Gly-Val-D-alloIle-Ser-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 270 is used but substituting Fmoc-D-alloIle for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Succinyl-Sar-Gly-Val-D-alloIle-Ser-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate.

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Example 282

N-Ac-Sar-Gly-Val-D-alloIle-Ser-Nva-Ile-Arg-ProNHCH(CH₃)₂

The procedure described in Example 276 is used but substituting Fmoc-D-alloIle for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-alloIle-Ser-Nva-Ile-Arg-ProNHCH(CH₃)₂ as the trifluoroacetate.

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Example 283

N-Ac-Sar-Gly-Val-D-alloIle-Ser-Nva-Ile-Arg-Pro-D-AlaNH₂

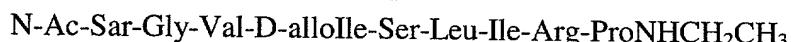
The procedure described in Example 268 is used but substituting Fmoc-D-alloIle for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column

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chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to N-Ac-Sar-Gly-Val-D-alloIle-Ser-Nva-Ile-Arg-Pro-D-AlaNH₂ as the trifluoroacetate.

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Example 284



The procedure described in Example 265 is used but substituting Fmoc-D-alloIle for Fmoc-D-Ile and Fmoc-Leu for Fmoc-Gln(Trt). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-alloIle-Ser-Leu-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate.

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Example 285

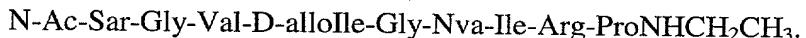


The procedure described in Example 276 is used but substituting Fmoc-D-alloIle for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-alloIle-Ser-Ser-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate.

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Example 286

The procedure described in Example 125 is used but separately substituting Fmoc-D-Ile and Fmoc-D-alloIle, respectively, for Fmoc-D-Leu. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to the the following peptides as trifluoroacetate salt:



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Example 287

The procedure described in Example 125 and 286 is used but separately substituting Fmoc-D-Ile and Fmoc-D-alloIle, respectively, for Fmoc-D-Leu and

substituting Fmoc-Gln(Trt) for Fmoc-Nva . After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield the trifluoroacetate salt of:

N-Ac-Sar-Gly-Val-D-Leu-Gly-Gln-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Gly-Gln-Ile-Arg-ProNHCH₂CH₃, and
N-Ac-Sar-Gly-Val-D-alloIle-Gly-Gln-Ile-Arg-ProNHCH₂CH₃.

10 Example 288

The procedure described in Example 123 is used but separately substituting Fmoc-D-Ile and Fmoc-D-alloIle, respectively, for Fmoc-D-Leu. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield the trifluoroacetate salt of:

N-Ac-Sar-Gly-Val-D-Ile-Tyr-Nva-Ile-Arg-ProNHCH₂CH₃ and
N-Ac-Sar-Gly-Val-D-alloIle-Tyr-Nva-Ile-Arg-ProNHCH₂CH₃.

20 Example 289

The procedure described in Example 123 and 288 is used but separately substituting Fmoc-D-Ile and Fmoc-D-alloIle, respectively, for Fmoc-D-Leu and substituting Fmoc-Gln(Trt) for Fmoc-Nva . After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield the trifluoroacetate salt of:

N-Ac-Sar-Gly-Val-D-Leu-Tyr-Gln-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Tyr-Gln-Ile-Arg-ProNHCH₂CH₃, and
N-Ac-Sar-Gly-Val-D-alloIle-Tyr-Gln-Ile-Arg-ProNHCH₂CH₃.

30 Example 290

N-Ac-Sar-Gly-Val-D-Ser-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 is used but substituting Fmoc-D-Ser(tBu) for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column

chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Ser-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate.

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Example 291

N-Ac-Sar-Gly-Val-D-Thr-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 is used but substituting Fmoc-D-Thr(tBu) for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Thr-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate.

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chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Thr-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate.

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Example 292

N-Ac-Sar-Gly-Val-D-Gln-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 is used but substituting Fmoc-D-Gln(Trt) for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Gln-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate.

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chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Gln-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate.

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Example 293

N-Ac-Sar-Gly-Val-D-Asn-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 is used but substituting Fmoc-D-Asn(Trt) for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Asn-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate.

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chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Asn-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate.

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Example 294

N-Ac-Sar-Gly-Val-D-Arg-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 is used but substituting Fmoc-D-Arg(Pmc) for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column

chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Arg-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate.

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Example 295

N-Ac-Sar-Gly-Val-D-3-Pal-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 is used but substituting Fmoc-D-3-Pal for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-3-Pal-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate.

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Example 296

N-Ac-Sar-Gly-Val-D-Glu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 is used but substituting Fmoc-D-Glu(OtBu)-OH for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Glu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate.

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Example 297

N-Ac-Sar-Gly-Val-D-Asp-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

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The procedure described in Example 1 is used but substituting Fmoc-D-Asp(OtBu)-OH for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Asp-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate.

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Example 298

N-Ac-Sar-Gly-Val-D-His-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

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The procedure described in Example 1 is used but substituting Fmoc-D-His(Boc)-

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OH for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18

column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-His-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate.

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Example 299

N-Ac-Sar-Gly-Val-D-Hser-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 is used but substituting Fmoc-D-Hser(tBu) for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Hser-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate.

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Example 300

N-Ac-Sar-Gly-Val-D-alloThr-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 is used but substituting Fmoc-D-alloThr(tBu) for Fmoc-D-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-alloThr-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate.

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Example 301

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-D-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 is used but substituting Fmoc-D-Ile for Fmoc-Ile. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-D-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate.

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Example 302

N-Ac-Sar-Gly-Val-D-Ser-Thr-Gln-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 290 is used but substituting Fmoc-Gln(Trt) for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column

chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Ser-Thr-Gln-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate.

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Example 303

N-Ac-Sar-Gly-Val-D-Thr-Thr-Gln-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 291 is used but substituting Fmoc-Gln(Trt) for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Thr-Thr-Gln-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate.

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Example 304

N-Ac-Sar-Gly-Val-D-alloThr-Thr-Gln-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 300 is used but substituting Fmoc-Gln(Trt) for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-alloThr-Thr-Gln-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate.

15

Example 305

N-Ac-Sar-Gly-Val-D-Ser-Ser-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 290 is used but substituting Fmoc-Ser(tBu) for Fmoc-Thr(tBu). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to N-Ac-Sar-Gly-Val-D-Ser-Ser-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate.

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Example 306

N-Ac-Sar-Gly-Val-D-Thr-Ser-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 291 is used but substituting Fmoc-Ser(tBu) for Fmoc-Thr(tBu). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18

column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Thr-Ser-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate.

Example 307

N-Ac-Sar-Gly-Val-D-alloThr-Ser-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 300 is used but substituting Fmoc-Ser(tBu) for Fmoc-Thr(tBu). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-alloThr-Ser-Nva-Ile-Arg-ProNH₂CH₂CH₃ as the trifluoroacetate.

Example 308

N-Ac-Sar-Gly-Val-D-alloThr-Ser-Gln-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 304 is used but substituting Fmoc-Gln(Trt) for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-alloThr-Ser-Gln-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate.

Example 309

N-Ac-Sar-Gly-Val-D-Thr-Ser-Gln-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 303 is used but substituting Fmoc-Gln(Trt) for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Thr-Ser-Gln-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate.

Example 310

The procedure described in Examples 132 and 266 is used but substituting N-acetyl-6-aminocaproic acid (6-Ac-Aca) for acetic acid. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying

in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield the following peptides as trifluoroacetate salt:

N-(6-Ac-Aca)-Sar-Gly-Val-D-Leu-Ser-Gln-Ile-Arg-ProNHCH(CH₃)₂, and
N-(6-Ac-Aca)-Sar-Gly-Val-D-Leu-Ser-Nva-Ile-Arg-ProNHCH(CH₃)₂.

5

Example 311

The procedure described in Examples 310 is used but substituting N-acetyl-gamma-aminobutyric acid (4-Ac-Gaba) instead of N-acetyl-6-aminocaproic acid. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield the following peptides as trifluoroacetate salt:

N-(4-Ac-Gaba)-Sar-Gly-Val-D-Leu-Ser-Gln-Ile-Arg-ProNHCH(CH₃)₂, and
N-(4-Ac-Gaba)-Sar-Gly-Val-D-Leu-Ser-Nva-Ile-Arg-ProNHCH(CH₃)₂.

15

Example 312

The procedure described in Examples 311 is used but substituting 2-furoic acid instead of N-acetyl-gamma-aminobutyric acid. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield the following peptides as trifluoroacetate salt:

N-(2-Furoyl)-Sar-Gly-Val-D-Leu-Ser-Gln-Ile-Arg-ProNHCH(CH₃)₂, and
N-(2-Furoyl)-Sar-Gly-Val-D-Leu-Ser-Nva-Ile-Arg-ProNHCH(CH₃)₂.

25

Example 313

The procedure described in Examples 311 is used but substituting shikimic acid instead of 2-furoic acid. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield the following peptides as trifluoroacetate salt:

N-(Shikimyl)-Sar-Gly-Val-D-Leu-Ser-Gln-Ile-Arg-ProNHCH(CH₃)₂, and
N-(Shikimyl)-Sar-Gly-Val-D-Leu-Ser-Nva-Ile-Arg-ProNHCH(CH₃)₂.

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Example 314

The procedure described in Examples 311 is substituting shikimic acid instead of 2-furoic acid. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield the following peptides as trifluoroacetate salt:

N-(Shikimyl)-Sar-Gly-Val-D-Leu-Ser-Gln-Ile-Arg-ProNHCH(CH₃)₂, and
N-(Shikimyl)-Sar-Gly-Val-D-Leu-Ser-Nva-Ile-Arg-ProNHCH(CH₃)₂.

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Example 315

The procedure described in Examples 312 is used but substituting 2-methyl-nicotinic acid instead of 2-furoic acid. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield the following peptides as trifluoroacetate salt:

N-(2-Me-nicotinyl)-Sar-Gly-Val-D-Leu-Ser-Gln-Ile-Arg-ProNHCH(CH₃)₂, and
N-(2-Me-nicotinyl)-Sar-Gly-Val-D-Leu-Ser-Nva-Ile-Arg-ProNHCH(CH₃)₂.

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Example 316

N-Ac-Sar-Gly-Val-D-Leu-Ser-Nva-Ile-Arg-ProNHethyl-1-(R)-cyclohexyl

The procedure described in Example 8 is used but substituting Fmoc-DLeu for Fmoc-DIle and Fmoc-Ser(tBu) for Fmoc-Thr(tBu). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Leu-Ser-Nva-Ile-Arg-ProNHethyl-1-(R)-cyclohexyl as the trifluoroacetate.

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Example 317

N-Ac-Sar-Gly-Val-DIle-Thr-Ser-Ile-Arg-ProNHethyl-1-(R)-cyclohexyl

The procedure described in Example 8 is used but substituting Fmoc-Ser(tBu) for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-

water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-DIle-Thr-Ser-Ile-Arg-ProNHethyl-1-(R)-cyclohexyl as the trifluoroacetate.

Example 318

5 N-Ac-Sar-Gly-Val-DIle-Thr-Leu-Ile-Arg-ProNHethyl-1-(R)-cyclohexyl

The procedure described in Example 8 is used but substituting Fmoc-Leu for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-
10 water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-DIle-Thr-Leu-Ile-Arg-ProNHethyl-1-(R)-cyclohexyl as the trifluoroacetate.

Example 319

15 N-Ac-Sar-Gly-Val-D-Leu-Thr-Nva-Ile-Arg-ProNHethyl-1-(R)-cyclohexyl

The procedure described in Example 8 is used but substituting Fmoc-D-Leu for Fmoc-DIle. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-
20 Val-D-Leu-Thr-Nva-Ile-Arg-ProNHethyl-1-(R)-cyclohexyl as the trifluoroacetate.

Example 320

N-Ac-Sar-Gly-Val-D-Leu-Ser-Ser-Ile-Arg-ProNHethyl-1-(R)-cyclohexyl

The procedure described in Example 316 is used but substituting Fmoc-Ser(tBu)
25 for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-
Val-D-Leu-Ser-Ser-Ile-Arg-ProNHethyl-1-(R)-cyclohexyl as the trifluoroacetate.

30

Example 321

N-Ac-Sar-Gly-Val-D-Leu-Ser-Gln-Ile-Arg-ProNHethyl-1-(R)-cyclohexyl

The procedure described in Example 316 is used but substituting Fmoc-Gln(Trt)
for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting
35 groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-

water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Leu-Ser-Gln-Ile-Arg-ProNHethyl-1-(R)-cyclohexyl as the trifluoroacetate.

Example 322

5 N-Ac-Sar-Gly-Val-DIle-Thr-Nva-Ile-Arg-ProNHethyl-1-(S)-cyclohexyl

The procedure described in Example 8 is used but substituting (S)-1-cycloxyethylamine for (R)-1-cycloxyethylamine. After cleavage of the peptide from the resin and removal of the protecting groups the crude product was purified by C-18 column chromatography using solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-10 Val-DIle-Thr-Nva-Ile-Arg-ProNHethyl-1-(S)-cyclohexyl as the trifluoroacetate salt.

Example 323

The procedures described in Example 98 is used but substituting the appropriate 15 protected amino acids as describes in Examples 132, 43, 54, and 75. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield the following peptides as trifluoroacetate salt:

20 N-Ac-Sar-Gly-Val-D-Pen-Ser-Nva-Ile-Arg-ProNHCH₂CH₃,

N-Ac-Sar-Gly-Val-D-Pen-Gly-Nva-Ile-Arg-ProNHCH₂CH₃,

N-Ac-Sar-Gly-Val-D-Pen-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,

N-Ac-Sar-Gly-Val-D-Pen-Ser-Nva-Ile-Arg-ProNHCH(CH₃)₂,

N-Succinyl-Sar-Gly-Val-D-Pen-Ser-Nva-Ile-Arg-ProNHCH₂CH₃,

25 N-Ac-Sar-Gly-Val-D-Pen-Ser-Nva-Ile-Arg-Pro-D-AlaNH₂,

N-Ac-Sar-Gly-Val-D-Pen-Ser-Gln-Ile-Arg-ProNHCH₂CH₃,

N-Ac-Sar-Gly-Val-D-Pen-Gly-Gln-Ile-Arg-ProNHCH₂CH₃,

N-Ac-Sar-Gly-Val-D-Pen-Ser-Ser-Ile-Arg-ProNHCH₂CH₃,

N-Ac-Sar-Gly-Val-D-Pen-Thr-Ser-Ile-Arg-ProNHCH₂CH₃,

30 N-Ac-Sar-Gly-Val-D-Pen-Thr-Leu-Ile-Arg-ProNHCH₂CH₃,

N-Ac-Sar-Gly-Val-D-Pen-Ser-Leu-Ile-Arg-ProNHCH₂CH₃,

N-Succinyl-Sar-Gly-Val-D-Pen-Ser-Ser-Ile-Arg-ProNHCH₂CH₃,

N-Succinyl-Sar-Gly-Val-D-Pen-Ser-Leu-Ile-Arg-ProNHCH₂CH₃, and

N-Succinyl-Sar-Gly-Val-D-Pen-Thr-Gln-Ile-Arg-ProNHCH(CH₃)₂.

35

Example 324

N-Ac-Sar-Gly-Val-D-Cys-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 98 is used but substituting Fmoc-D-Cys(Trt) for Fmoc-D-Pen(Trt). After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield N-Ac-Sar-Gly-Val-D-Cys-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate.

Example 325

The procedures described in Example 324 is used but substituting the appropriate protected amino acids as describes in Examples 132, 43, 54, and 75. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield the following peptides as trifluoroacetate salt:

N-Ac-Sar-Gly-Val-D-Cys-Ser-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Cys-Gly-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Cys-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Cys-Ser-Nva-Ile-Arg-ProNHCH(CH₃)₂,
N-Succinyl-Sar-Gly-Val-D-Cys-Ser-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Cys-Ser-Nva-Ile-Arg-Pro-D-AlaNH₂,
N-Ac-Sar-Gly-Val-D-Cys-Ser-Gln-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Cys-Gly-Gln-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Cys-Ser-Ser-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Cys-Thr-Ser-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Cys-Thr-Leu-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Cys-Ser-Leu-Ile-Arg-ProNHCH₂CH₃,
N-Succinyl-Sar-Gly-Val-D-Cys-Ser-Ser-Ile-Arg-ProNHCH₂CH₃, and
N-Succinyl-Sar-Gly-Val-D-Cys-Ser-Leu-Ile-Arg-ProNHCH₂CH₃.

Example 326

N-Ac-Sar-Gly-Pen-DIle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 is used but substituting Fmoc-Pen(Trt) for Fmoc-Val. After cleavage of the peptide from the resin and removal of the protecting groups the crude product was purified by C-18 column chromatography using solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA.

The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Pen-DIle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt.

Example 327

5 N-Ac-Sar-Gly-Cys-DIle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 1 is used but substituting Fmoc-Cys(Trt) for Fmoc-Val. After cleavage of the peptide from the resin and removal of the protecting groups the crude product was purified by C-18 column chromatography using solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA.

10 The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Cys-DIle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt.

Example 328

15 The procedures described in Example 326 is used but substituting the appropriate protected amino acids as describes in Examples 14, 15, 132, 43, 54, and 75. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield the following peptides as trifluoroacetate

20 salt:

N-Ac-Sar-Gly-Pen-D-alloIle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,

N-Ac-Sar-Gly-Pen-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,

N-Ac-Sar-Gly-Pen-D-Ile-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,

N-Ac-Sar-Gly-Pen-D-Ile-Ser-Nva-Ile-Arg-ProNHCH₂CH₃,

25 N-Ac-Sar-Gly-Pen-D-Ile-Thr-Nva-Ile-Arg-ProNHCH(CH₃)₂,

N-Ac-Sar-Gly-Pen-D-Ile-Thr-Nva-Ile-Arg-Pro-D-AlaNH₂,

N-Succinyl-Gly-Pen-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,

N-Succinyl-Sar-Gly-Pen-D-Ile-Thr-Gln-Ile-Arg-ProNHCH₂CH₃, and

30 N-Succinyl-Sar-Gly-Pen-D-Ile-Thr-Gln-Ile-Arg-ProNHCH(CH₃)₂.

Example 329

N-Ac-Sar-Gly-Val-D-Leu-Pen-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in Example 120 is used but substituting Fmoc-Pen(Trt)

for Fmoc-Ala. After cleavage of the peptide from the resin and removal of the protecting groups the crude product was purified by C-18 column chromatography using solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA.

The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Leu-Pen-Nva-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt.

Example 330

5 The procedures described in Example 329 is used but substituting the appropriate
protected amino acids as describes in Examples 14, 15, 132, 43, 54, and 75. After
cleavage of the peptide from the resin and removal of the protecting groups using (9:1)
TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a
solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01%
10 TFA. The pure fractions are lyophilized to yield the following peptides as trifluoroacetate
salt:

N-Ac-Sar-Gly-Val-D-Ile-Pen-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-alloIle-Pen-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Pen-Gln-Ile-Arg-ProNHCH₂CH₃,
15 N-Ac-Sar-Gly-Val-D-Ile-Pen-Ser-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Pen-Leu-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Pen-Nva-Ile-Arg-ProNHCH(CH₃)₂,
N-Ac-Sar-Gly-Val-D-Ile-Pen-Nva-Ile-Arg-Pro-D-AlaNH₂,
N-Succinyl-Sar-Gly-Val-D-Ile-Pen-Nva-Ile-Arg-ProNHCH₂CH₃,
20 N-Succinyl-Sar-Gly-Val-D-Ile-Pen-Gln-Ile-Arg-ProNHCH₂CH₃, and
N-Succinyl-Sar-Gly-Val-D-Ile-Pen-Gln-Ile-Arg-ProNHCH(CH₃)₂.

Example 331

N-Ac-Sar-Gly-Val-D-Ile-Thr-Pen-Ile-Arg-ProNHCH₂CH₃

25 The procedure described in Example 11 is used but substituting Fmoc-Pen(Trt) for
Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting
groups the crude product was purified by C-18 column chromatography using solvent
mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA.
The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Pen-Ile-Arg-
30 ProNHCH₂CH₃ as the trifluoroacetate salt.

Example 332

The procedures described in Example 331 is used but substituting the appropriate
protected amino acids as describes in Examples 14, 15, 132, 43, 54, and 75. After
35 cleavage of the peptide from the resin and removal of the protecting groups using (9:1)
TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a

solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield the following peptides as trifluoroacetate salt:

5 N-Ac-Sar-Gly-Val-D-alloIle-Thr-Pen-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Leu-Thr-Pen-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Pen-Ile-Arg-Pro-D-AlaNH₂,
N-Succinyl-Sar-Gly-Val-D-Ile-Thr-Pen-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Ile-Thr-Pen-Ile-Arg-ProNHCH(CH₃)₂,
N-Ac-Sar-Gly-Val-D-Leu-Ser-Pen-Ile-Arg-ProNHCH₂CH₃,
10 N-Ac-Sar-Gly-Val-D-Leu-Gly-Pen-Ile-Arg-ProNHCH₂CH₃, and
N-Succinyl-Sar-Gly-Val-D-Leu-Ser-Pen-Ile-Arg-ProNHCH₂CH₃.

Example 333

N-Ac-Sar-Gly-Val-D-Phe(3,4,5-triF)-Thr-Gln-Ile-Arg-ProNHCH₂CH₃

15 The procedure described in Example 96 is used but substituting Fmoc-Gln(Trt) for Fmoc-Nva. After cleavage of the peptide from the resin and removal of the protecting groups the crude product was purified by C-18 column chromatography using solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Phe(3,4,5-triF)-Thr-Gln-Ile-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt.

Example 334

The procedures described in Example 333 is used but substituting the appropriate protected amino acids as describes in Examples 132, 43, 54, and 75. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield the following peptides as trifluoroacetate salt:

30 N-Ac-Sar-Gly-Val-D-Phe(3,4,5-triF)-Ser-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Phe(3,4,5-triF)-Gly-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Phe(3,4,5-triF)-Ser-Leu-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Gly-Val-D-Phe(3,4,5-triF)-Ser-Nva-Ile-Arg-Pro-D-AlaNH₂,
N-Succinyl-Sar-Gly-Val-D-Phe(3,4,5-triF)-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
N-Succinyl-Sar-Gly-Val-D-Phe(3,4,5-triF)-Ser-Gln-Ile-Arg-ProNHCH₂CH₃,
35 N-Succinyl-Sar-Gly-Val-D-Phe(3,4,5-triF)-Thr-Gln-Ile-Arg-ProNHCH(CH₃)₂,
N-Ac-Sar-Gly-Val-D-Phe(3,4,5-triF)-Ser-Gln-Ile-Arg-ProNHCH₂CH₃, and

N-Ac-Sar-Gly-Val-D-Phe(3,4,5-triF)-Ser-Ser-Ile-Arg-ProNHCH₂CH₃.

Example 335

N-Ac-Sar-Ala-Val-D-alloIle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

5 The procedure described in Example 153 is used but substituting Fmoc-DalloIle
for Fmoc-DIle. After cleavage of the peptide from the resin and removal of the protecting
groups the crude product was purified by C-18 column chromatography using solvent
mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA.
The pure fractions were lyophilized to yield N-Ac-Sar-Ala-Val-D-alloIle-Thr-Nva-Ile-Arg-
10 ProNHCH₂CH₃ as the trifluoroacetate salt.

Example 336

The procedures described in Example 335 is used but substituting the appropriate
protected amino acids as described in Examples 132, 43, 54, and 75. After cleavage of the
15 peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3
mL) the crude product is purified by C-18 column chromatography using a solvent mixture
varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure
fractions are lyophilized to yield the following peptides as trifluoroacetate salt:

20 N-Ac-Sar-Ala-Val-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Ala-Val-D-Ile-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Ala-Val-D-Leu-Ser-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Ac-Sar-Ala-Val-D-Leu-Ser-Gln-Ile-Arg-ProNHCH₂CH₃,
N-Succinyl-Sar-Ala-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-Succinyl-Sar-Ala-Val-D-Ile-Thr-Gln-Nva-Ile-Arg-ProNHCH₂CH₃,
25 N-Succinyl-Sar-Ala-Val-D-Ile-Thr-Gln-Nva-Ile-Arg-ProNHCH(CH₃)₂, and
N-Succinyl-Sar-Ala-Val-D-Ile-Thr-Gln-Nva-Ile-Arg-Pro-D-AlaNH₂.

Example 337

The procedure described in Example 231 used but substituting N-acetyl-beta-
30 alanine (3-Ac-Bala) for N-acetyl-4-aminobutyric acid. After cleavage of the peptide from
the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude
product is purified by C-18 column chromatography using a solvent mixture varying in a
gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are
lyophilized to yield the following peptides as trifluoroacetate salt:

35 N-(3-Ac-Bala)-Sar-Gly-Val-D-alloIle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-(3-Ac-Bala)-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,

N-(3-Ac-Bala)-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH₂CH₃,
N-(3-Ac-Bala)-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-Pro-D-AlaNH₂,
N-(3-Ac-Bala)-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-Pro-DAlaNH₂,
N-(3-Ac-Bala)-Sar-Gly-Val-D-alloIle-Thr-Gln-Ile-Arg-ProNHCH(CH₃)₂,
5 N-(3-Ac-Bala)-Sar-Gly-Val-D-Leu-Ser-Nva-Ile-Arg-ProNHCH₂CH₃,
N-(3-Ac-Bala)-Sar-Gly-Val-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-(3-Ac-Bala)-Sar-Gly-Val-D-Pen-Thr-Nva-Ile-Arg-ProNHCH₂CH₃,
N-(3-Ac-Bala)-Sar-Gly-Val-D-Ile-Ser-Nva-Ile-Arg-ProNHCH₂CH₃,
N-(3-Ac-Bala)-Sar-Ala-Val-D-alloIle-Ser-Nva-Ile-Arg-ProNHCH₂CH₃,
10 N-(3-Ac-Bala)-Sar-Ala-Val-D-Ile-Ser-Nva-Ile-Arg-ProNHCH₂CH₃,
N-(3-Ac-Bala)-Sar-Ala-Val-D-Leu-Ser-Nva-Ile-Arg-ProNHCH₂CH₃, and
N-(3-Ac-Bala)-Sar-Ala-Val-D-Leu-Ser-Gln-Ile-Arg-ProNHCH₂CH₃.

Example 338

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Pro-OH

The procedure described in Example 1 is used but substituting omitting the coupling with ethylamine. After cleavage of the peptide from the resin and removal of the protecting groups the crude product was purified by C-18 column chromatography using solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Pro-OH as the trifluoroacetate salt.

Example 339

The procedures described in Example 338 is used but substituting the appropriate protected amino acids as described in Examples 14, 15, 132, 43, 54, and 75. After cleavage of the peptide from the resin and removal of the protecting groups using (9:1) TFA/anisole (3 mL) the crude product is purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.01% TFA. The pure fractions are lyophilized to yield the following peptides as trifluoroacetate salt:

N-Ac-Sar-Gly-Val-D-alloIle-Thr-Nva-Ile-Arg-Pro-OH,
N-Ac-Sar-Gly-Val-D-Leu-Thr-Nva-Ile-Arg-Pro-OH,
N-Ac-Sar-Gly-Val-D-Pen-Thr-Nva-Ile-Arg-Pro-OH,
N-Ac-Sar-Gly-Val-D-Phe(3,4,5-triF)-Thr-Nva-Ile-Arg-Pro-OH,
35 N-Ac-Sar-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-Pro-OH,
N-Ac-Sar-Gly-Val-D-Leu-Ser-Nva-Ile-Arg-Pro-OH,

N-Ac-Sar-Ala-Val-D-Ile-Thr-Nva-Ile-Arg-Pro-OH,
N-Ac-Sar-Gly-Val-D-Ile-Ser-Gln-Ile-Arg-Pro-OH,
N-Succinyl-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Pro-OH, and
N-Succinyl-Sar-Gly-Val-D-Leu-Thr-Gln-Ile-Arg-Pro-OH.

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Example 340

N-Ac-Sar-Gly-Asp-D-Leu-Thr-Nva-Ile-Arg-ProNH₂CH₂CH₃

In an Applied Biosystems 433A peptide synthesizer, 0.1 mM of Fmoc-Pro-Sieber ethylamide resin was placed in the reaction vessel and cartridges of 1 mM amino acids 10 were sequentially loaded. The Fastmoc 0.1 with previous peak monitoring protocol was used. The following is the synthetic cycle:

1. Solvating resin with N-methylpyrrolidone (NMP) for about 5 minutes;
2. Washing with NMP for about 5 minutes;
3. Removing the Fmoc group using 50% piperidine solution in NMP for 5 minutes, 15 washing and repeating the process 3 to 4 times;
4. Activating the Fmoc-amino acid using 1 mM of 0.5 M solution of 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) in DMF;
5. Adding the activated Fmoc-amino acid to the reaction vessel followed by 1 mM 20 of 2 M diisopropylamine in NMP solution;
6. Coupling of the Fmoc-amino acid for 20 minutes;
7. Washing and removal of Fmoc-group using 50 % piperidine in NMP.

The following protected amino acids were sequentially coupled to the resin using above protocol in Table 2, below:

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Table 2

Amino acid	Coupling time
1. Fmoc-Arg(Pmc)	20 minutes
2. Fmoc-Ile	20 minutes
3. Fmoc-Nva	20 minutes
4. Fmoc-Thr(<i>t</i> -Bu)	20 minutes
5. Fmoc-D-Leu	20 minutes
6. Fmoc-Asp(OtBu)	20 minutes
7. Fmoc-Gly	20 minutes
8. Fmoc-Sar	20 minutes
9. acetic acid	20 minutes

Upon completion of the synthesis the resin-bound peptide was washed with methanol three times and dried *in vacuo*, then treated with a (95:5) TFA/water solution (3mL) at room temperature overnight. The resin was filtered and washed 3 times with methanol. The filtrates and the washes were combined and concentrated *in vacuo*. The residue was treated with ether and the precipitate was filtered to give the crude peptide as amorphous powder. This was purified by preparative HPLC using C-18 column with a mixture of solvents varying in a gradient from 5 % to 100 % acetonitrile/water containing 0.1% TFA over a period of 50 min. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Asp-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as trifluoroacetate salt; R_t = 2.23 min (using C-18 column and solvents mixture varying in a gradient from 20 % to 95 % acetonitrile/water containing 10 mM ammonium acetate over a period of 10 min); MS (ESI) m/e 1010 (M⁺).

Example 341

N-Ac-Sar-Gly-Ala-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in example 340 was used but substituting Fmoc-Ala for Fmoc-Asp(OtBu). After cleavage of the peptide from the resin and removal of the protecting groups the product was precipitated with ether. The crude compound was purified by preparative HPLC to give N-Ac-Sar-Gly-Ala-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as trifluoroacetate salt; R_t = 2.828 min (using C-18 column and solvents mixture varying in a gradient from 20 % to 95 % acetonitrile/water containing 10 mM ammonium acetate over a period of 10 min); MS (ESI) m/e 966 (M⁺).

Example 342

N-Ac-Sar-Gly-Cha-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in example 340 was used but substituting Fmoc-Cha for Fmoc-Asp(OtBu). After cleavage of the peptide from the resin and removal of the protecting groups the product was precipitated with ether. The crude compound was purified by preparative HPLC to give N-Ac-Sar-Gly-Cha-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as trifluoroacetate salt; R_t = 4.48 min (using C-18 column and solvents mixture varying in a gradient from 20 % to 95 % acetonitrile/water containing 10 mM ammonium acetate over a period of 10 min); MS (ESI) m/e 1048 (M⁺).

Example 343

N-Ac-Sar-Gly-Met-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in example 340 was used but substituting Fmoc-Met for Fmoc-Asp(OtBu) and Fmoc-D-Ile for Fmoc-D-Leu. After cleavage of the peptide from the resin and removal of the protecting groups the product was precipitated with ether. The crude compound was purified by preparative HPLC to give N-Ac-Sar-Gly-Met-D-Ile-
5 Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as trifluoroacetate salt; R_t = 3.25 min (using C-18 column and solvents mixture varying in a gradient from 20 % to 95 % acetonitrile/water containing 10 mM ammonium acetate over a period of 10 min); MS (ESI) m/e 1026 (M+H); Amino Acid Anal.: 1.09 Sar; 0.97 Gly; 0.94 Met; 2.08 Ile; 0.47 Thr; 1.00 Nva; 1.34 Arg; 1.01 Pro.

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Example 344
N-Ac-Cit-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in example 340 was used but substituting Fmoc-Cit for Fmoc-Sar, Fmoc-Val for Fmoc-Asp(OtBu) and Fmoc-D-Ile for Fmoc-D-Leu. After 15 cleavage of the peptide from the resin and removal of the protecting groups the product was precipitated with ether. The crude compound was purified by preparative HPLC to N-Ac-Cit-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃ as trifluoroacetate salt; R_t = 2.97 min (using C-18 column and solvents mixture varying in a gradient from 20 % to 95 % acetonitrile/water containing 10 mM ammonium acetate over a period of 10 min); MS 20 (ESI) m/e 1080 (M+H); Amino Acid Anal.: 0.98 Cit; 0.93 Gly; 0.98 Val; 2.05 Ile; 0.51 Thr; 0.99 Nva; 1.37 Arg; 1.01 Pro.

Example 345
N-Ac-Sar-Gly-Val-D-Ile-Thr-Hser-Ile-Arg-ProNHCH₂CH₃

The procedure described in example 340 was used but substituting Fmoc-Hser(t-Bu) for Fmoc-Nva, Fmoc-Val for Fmoc-Asp(OtBu), and Fmoc-D-Ile for Fmoc-D-Leu. After 25 cleavage of the peptide from the resin and removal of the protecting groups the product was precipitated with ether. The crude compound was purified by preparative HPLC to give N-Ac-Sar-Gly-Val-D-Ile-Thr-Hser-Ile-Arg-ProNHCH₂CH₃ as trifluoroacetate salt; R_t = 2.782 min (using C-18 column and solvents mixture varying in a 30 gradient from 10 % to 40 % acetonitrile/water containing 0.1 % TFA over a period of 33 min); MS (ESI) m/e 996 (M+H); Amino Acid Anal.: 1.00 Sar; 0.95 Gly; 1.01 Val; 1.99 Ile; 0.60 Thr; 1.07 Arg; 1.04 Pro.

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Example 346
N-Ac-Sar-Gly-Val-D-alloIle-His-Nva-Ile-Arg-ProNHCH₂CH₃

The procedure described in example 340 was used but substituting Fmoc-Val for Fmoc-Asp(OtBu), Fmoc-D-alloIle for Fmoc-D-Leu, and Fmoc-His(Boc) for Fmoc-Thr(*t*-Bu). After cleavage of the peptide from the resin and removal of the protecting groups the product was precipitated with ether. The crude compound was purified by preparative
5 HPLC to give N-Ac-Sar-Gly-Val-Dallole-His-Nva-Ile-Arg-ProNHCH₂CH₃ as a trifluoroacetate salt; R_t = 3.12 min (using C-18 column and solvents mixture varying in a gradient from 10 % to 40 % acetonitrile/water containing 0.1 % TFA over a period of 33 min); MS (ESI) m/e 1030 (M⁺).

10 Example 347

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNH-n-Butyl

Resin Preparation

4-(4-Formyl-3-methoxyphenoxy)butyryl AM resin (0.5 g, 0.54 mmol/g substitution) was placed in a solid phase synthesis reaction vessel containing (9:1) DMA/acetic acid (4 mL). The mixture was shaken for 5 min. The resin was drained and this process was repeated three times. To the swollen resin were added 10-15 grains of activated 4A molecular sieves and (9:1) DMA/acetic acid (4mL) and 10 molar equivalents of n-butylamine. The slurry was shaken for 1h at rt and to it was added 10 molar equivalents of sodium triacetoxyborohydride. The slurry was shaken for 2 h at rt. The resin was drained and washed three times with DMA, three times with methanol, three times with dichloromethane, three times with diethyl ether and dried *in vacuo* at rt overnight. The dry resin was swollen in DMA (4 mL) and shaken for 5 min. This process was repeated twice.

Coupling of Fmoc-Pro

25 To the swollen resin in the reaction vessel were added sequentially the following chemicals: DMA (4 mL), one equivalent of DIEA, a DMA solution containing 3.0 equivalents of Fmoc-Pro, 3.0 equivalents of HATU, and 3.0 equivalents of DIEA. The slurry was shaken overnight. The resin was drained and washed three times with DMA, three times with methanol, three times with dichloromethane, three times with diethyl ether and dried *in vacuo* at rt overnight. A small portion of the resin was used to determine the Fmoc-Pro loading. The rest of the resin was shaken with DMA (4 mL) three times for 5 min and then for 1 h at rt with a solution of (8:1:1) DMA/pyridine/acetic anhydride (5 mL). The resin was drained and washed three times with DMA, three times with methanol, three times with dichloromethane, and three times with diethyl ether. The resin was dried *in vacuo* at rt overnight and then used in the subsequent solid phase peptide synthesis.

Synthesis of Peptide

In the synthesis of the above peptide, the amino acids, the coupling conditions and the synthetic protocol used were identical to those described in Example 340. Upon completion of the synthesis the peptide and the protecting groups were cleaved at rt using (95:5) TFA/water (3 mL) for 3h. The resin was filtered and washed three times with methanol. The combined filtrates were concentrated *in vacuo* and to the residue was added diethylether. The solid precipitate was filtered. The crude product was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.1% TFA. The pure fractions were lyophilized to yield NAcSar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNH-n-Butyl as the trifluoroacetate salt: $R_t = 3.792$ min (gradient of 20% to 95% acetonitrile in water containing 0.01 M NH₄Ac over 10 min period); MS (ESI) m/e 1022 (M⁺).

Example 348

15 N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNH-iso-Butyl

The procedure described in example 347 was used but substituting isobutylamine for n-butylamine. After cleavage of the peptide from the resin and precipitation with ether the crude product was obtained. This was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.1% TFA. The pure fractions were lyophilized to NAcSar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNH-iso-Butyl as the trifluoroacetate salt: $R_t = 3.731$ min (gradient of 20% to 95% acetonitrile in water containing 0.01 M NH₄Ac over 10 min period); MS (ESI) m/e 1022 (M⁺).

Example 349

25 N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNH-iso-Amyl

The procedure described in example 347 was used but substituting isoamylamine for n-butylamine. After cleavage of the peptide from the resin and precipitation with ether the crude product was obtained. This was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.1% TFA. The pure fractions were lyophilized to NAcSar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNH-iso-Amyl as the trifluoroacetate salt: $R_t = 4.086$ min (gradient of 20% to 95% acetonitrile in water containing 0.01 M NH₄Ac over 10 min period); MS (ESI) m/e 1036 (M⁺).

35 Example 350

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNH-n-hexyl

The procedure described in example 347 was used but substituting in n-hexylamine for n-butylamine. After cleavage of the peptide from the resin and precipitation with ether the crude product was obtained. This was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.1% TFA. The pure fractions were lyophilized to NAcSar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNH-n-Hexyl as the trifluoroacetate salt: $R_t = 4.527\text{min}$ (gradient of 20% to 95% acetonitrile in water containing 0.01 M NH₄Ac over 10 min period); MS (ESI) m/e 1050 (M^+).

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Example 351

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNH-(3,3-dimethyl)butyl

The procedure described in example 347 was used but substituting (3,3-dimethyl)butylamine for n-butylamine. After cleavage of the peptide from the resin and precipitation with ether the crude product was obtained. This was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.1% TFA. The pure fractions were lyophilized to NAcSar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNH-(3,3-dimethyl)butyl as the trifluoroacetate salt: $R_t = 4.366\text{min}$ (gradient of 20% to 95% acetonitrile in water containing 0.01 M NH₄Ac over 10 min period); MS (ESI) m/e 1050 (M^+).

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Example 352

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNH-(2-ethoxy)ethyl

The procedure described in example 347 was used but substituting (2-ethoxy)ethylamine for n-butylamine. After cleavage of the peptide from the resin and precipitation with ether the crude product was obtained. This was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.1% TFA. The pure fractions were lyophilized to NAcSar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNH-(2-ethoxy)ethyl as the trifluoroacetate salt: $R_t = 3.356\text{ min}$ (gradient of 20% to 95% acetonitrile in water containing 0.01 M NH₄Ac over 10 min period); MS (ESI) m/e 1038 (M^+).

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Example 353

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNH-(2-isopropoxy)ethyl

The procedure described in example 347 was used but substituting (2-isopropoxy)ethylamine for n-butylamine. After cleavage of the peptide from the resin and

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precipitation with ether the crude product was obtained. This was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.1% TFA. The pure fractions were lyophilized to NAcSar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg- ProNH-(2-isopropoxy)ethyl as the trifluoroacetate salt: R_t = 3.57 min (gradient of 20% to 95% acetonitrile in water containing 0.01 M NH₄Ac over 10 min period); MS (ESI) m/e 1052 (M⁺).

Example 354

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNH-(3-methoxy)propyl

The procedure described in example 347 was used but substituting (3-methoxy)propylamine for n-butylamine. After cleavage of the peptide from the resin and precipitation with ether the crude product was obtained. This was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.1% TFA. The pure fractions were lyophilized to NAcSar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg- ProNH-(3-methoxy)propyl as the trifluoroacetate salt: R_t = 3.26 min (gradient of 20% to 95% acetonitrile in water containing 0.01 M NH₄Ac over 10 min period); MS (ESI) m/e 1038 (M⁺).

Example 355

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNH-(cyclopentyl)methyl

The procedure described in example 347 was used but substituting (cyclopentyl)methylamine for n-butylamine. After cleavage of the peptide from the resin and precipitation with ether the crude product was obtained. This was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.1% TFA. The pure fractions were lyophilized to NAcSar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg- ProNH-(cyclopentyl)methyl as the trifluoroacetate salt: R_t = 4.148 min (gradient of 20% to 95% acetonitrile in water containing 0.01 M NH₄Ac over 10 min period); MS (ESI) m/e 1048 (M⁺).

Example 356

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNH-cyclohexyl

The procedure described in example 347 was used but substituting cyclohexylamine for n-butylamine. After cleavage of the peptide from the resin and precipitation with ether the crude product was obtained. This was purified by C-18 column chromatography using a solvent mixture varying in a gradient of 10% to 50% acetonitrile-water containing 0.1% TFA. The pure fractions were lyophilized to NAcSar-

Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNH-cyclohexyl as the trifluoroacetate salt: $R_t = 4.070$ min (gradient of 20% to 95% acetonitrile in water containing 0.01 M NH₄Ac over 10 min period); MS (ESI) m/e 1048 (M^+).

Example 357

5 N-Ac-Sar-Gly-Gln-DIle-Thr-Nva-Ile-Arg-Pro-DAlaNH₂

The procedure described in example 75 was used but substituting Fmoc-Gln(Trt) for Fmoc-Val. After cleavage of the peptide from the resin using (95:5) TFA/water solution and work-up, the crude product was purified by HPLC using C-18 column and eluting with a solvent mixture varying in a gradient from 5% to 100% acetonitrile/water containing 0.01% TFA over a period of 50 min. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Gln-DIle-Thr-Nva-Ile-Arg-Pro-DAlaNH₂ as the trifluoroacetate salt: $R_t = 2.15$ min (10% to 40% acetonitrile in water containing 0.01% of TFA, over 30 min period); MS (ESI) m/e 1066. ($M+H^+$); Amino Acid Anal.: 0.89 Sar; 0.94 Gly; 0.94 Glu; 2.06 Ile; 0.50 Thr; 1.08 Nva; 1.11 Arg; 1.03 Pro; 1.02 Ala.

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Example 358

N-Ac-Sar-Gly-Phe-DIle-Thr-Nva-Ile-Arg-Pro-DAlaNH₂

The procedure described in example 357 was used but substituting Fmoc-Phe for Fmoc-Gln(Trt). After cleavage of the peptide from the resin using (95:5) TFA/water solution and work-up, the crude product was purified by HPLC using C-18 column and eluting with a solvent mixture varying in a gradient from 5% to 100% acetonitrile/water containing 0.01% TFA over a period of 50 min. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Phe-DIle-Thr-Nva-Ile-Arg-Pro-DAlaNH₂ as the trifluoroacetate salt: $R_t = 3.565$ min (10% to 40% acetonitrile in water containing 0.01% of TFA, over 30 min period); MS (ESI) m/e 1085. ($M+H^+$); Amino Acid Anal.: 0.88 Sar; 1.01 Gly; 0.91 Phe; 1.97 Ile; 0.31 Thr; 0.89 Nva; 1.06 Arg; 1.05 Pro; 1.03 Ala.

Example 359

N-Ac-Sar-Gln-Val-DIle-Thr-Nva-Ile-Arg-ProNHEt

30 The procedure described in example 10 was used but substituting Fmoc-Pro-Sieber ethylamide resin for Fmoc-Pro-Sieber amide resin and Fmoc-Gln(Trt) for Fmoc-Gly. After cleavage of the peptide from the resin using (95:5) TFA/water solution and work-up, the crude product was purified by HPLC using C-18 column and eluting with a solvent mixture varying in a gradient from 5% to 100% acetonitrile/water containing 0.01% TFA over a period of 50 min. The pure fractions were lyophilized to yield N-Ac-Sar-Gln-Val-DIle-Thr-Nva-Ile-Arg-ProNHEt as the trifluoroacetate salt: $R_t = 3.06$ min (10% to 40%

acetonitrile in water containing 0.01% of TFA, over 30 min period); MS (ESI) m/e 1065 (M+H)⁺; Amino Acid Anal.: 0.92 Sar; 0.90 Gln; 1.01 Val; 2.07 Ile; 0.57 Thr; 1.03 Nva; 1.36 Arg; 1.10 Pro.

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Example 360

N-Ac-Sar-Gly-Val-DIle-alloThr-Nva-Ile-Arg-ProNHEt

The procedure described in example 359 was used but substituting Fmoc-Gly for Fmoc-Gln(Trt) and Fmoc-alloThr(tBu) for Fmoc-Thr(tBu). After cleavage of the peptide from the resin using (95:5) TFA/water solution and work-up, the crude product was purified by HPLC using C-18 column and eluting with a solvent mixture varying in a gradient from 5% to 100% acetonitrile/water containing 0.01% TFA over a period of 50 min. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-DIle-alloThr-Nva-Ile-Arg-ProNHEt as the trifluoroacetate salt: R_t = 3.52 min (10% to 40% acetonitrile in water containing 0.01% of TFA, over 30 min period); MS (ESI) m/e 994 (M+H)⁺; Amino Acid Anal.: 1.01 Sar; 1.00 Gly; 0.97 Val; 2.10 Ile; 0.58 Thr; 0.98 Nva; 1.0 Arg; 1.07 Pro.

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Example 361

N-Ac-Sar-Gly-Val-DIle-Thr-Nva-DIle-Arg-ProNHEt

The procedure described in example 360 was used but substituting Fmoc-Thr(tBu) for Fmoc-alloThr(tBu) and Fmoc-DIle for Fmoc-Ile. After cleavage of the peptide from the resin using (95:5) TFA/water solution and work-up, the crude product was purified by HPLC using C-18 column and eluting with a solvent mixture varying in a gradient from 5% to 100% acetonitrile/water containing 0.01% TFA over a period of 50 min. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-DIle-Thr-Nva-DIle-Arg-ProNHEt as the trifluoroacetate salt: R_t = 3.73 min (10% to 40% acetonitrile in water containing 0.01% of TFA, over 30 min period); MS (ESI) m/e 994 (M+H)⁺; Amino Acid Anal.: 1.03 Sar; 0.99 Gly; 0.97 Val; 2.11 Ile; 0.45 Thr; 1.04 Nva; 0.97 Arg; 1.04 Pro.

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Example 362N-Ac-Sar-Gly-Asn-DLeu-Ser-Nva-Ile-Arg-ProNHEt

The procedure described in example 360 was used but substituting Fmoc-Asn(Trt) for Fmoc-Val, Fmoc-DLeu for Fmoc-DIle, Fmoc-Ser(tBu) for Fmoc-alloThr(tBu). After cleavage of the peptide from the resin using (95:5) TFA/water solution and work-up, the crude product was purified by HPLC using C-18 column and eluting with a solvent mixture varying in a gradient from 5% to 100% acetonitrile/water containing 0.01% TFA over a period of 50 min. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Asn-DLeu-Ser-Nva-Ile-Arg-ProNHEt as the trifluoroacetate salt: R_t = 2.798 min (10% to 40%

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acetonitrile in water containing 0.01% of TFA, over 30 min period); MS (ESI) m/e 995 ($M+H$)⁺; Amino Acid Anal.: 0.94 Sar; 0.98 Gly; 0.99 Asp; 1.05 Leu; 0.26 Ser; 0.94 Nva; 0.95 Ile; 1.0 Arg; 1.09 Pro.

Example 363

N-(6-Me-Nicotinyl)-Sar-Gly-Val-DIle-Thr-Nva-Ile-Arg-ProNHEt

The procedure described in example 53 was used but substituting 6-Me-nicotinic acid for 2-Me-nicotinic acid. After cleavage of the peptide from the resin using (95:5) TFA/water solution and work-up, the crude product was purified by HPLC using C-18 column and eluting with a solvent mixture varying in a gradient from 5% to 100% acetonitrile/water containing 0.01% TFA over a period of 50 min. The pure fractions were lyophilized to yield N-(6-Me-Nicotinyl)-Sar-Gly-Val-DIle-Thr-Nva-DIle-Arg-ProNHEt as the trifluoroacetate salt: R_t = 3.82 min (10% to 40% acetonitrile in water containing 0.01% of TFA, over 30 min period); MS (ESI) m/e 1071 ($M+H^+$); Amino Acid Anal.: 0.98 Sar; 1.02 Gly; 1.01 Val; 2.05 Ile; 0.51 Thr; 1.01 Nva; 1.00 Arg; 1.08 Pro.

Example 364

N-Ac-Sar-Gly-Val-Ile-Thr-Nva-DIle-Arg-ProNHEt

The procedure described in example 1 was used but substituting Fmoc-Ile for Fmoc-DIle and Fmoc-DIle for Fmoc-Ile. After cleavage of the peptide from the resin using (95:5) TFA/water solution and work-up, the crude product was purified by HPLC using C-18 column and eluting with a solvent mixture varying in a gradient from 5% to 100% acetonitrile/water containing 0.01% TFA over a period of 50 min. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-Ile-Thr-Nva-DIle-Arg-ProNHEt as the trifluoroacetate salt: R_t = 3.62 min (10% to 40% acetonitrile in water containing 0.01% of TFA, over 30 min period); MS (ESI) m/e 994 ($M+H$)⁺; Amino Acid Anal.: 1.03 Sar; 1.03 Gly; 0.96 Val; 2.12 Ile; 0.43 Thr; 1.02 Nva; 1.02 Arg; 1.02 Pro.

Example 365

N-Ac-Sar-Gly-Val-DalloIle-Ser-Thr-Ile-Arg-ProNHEt

The procedure described in example 1 was used but substituting Fmoc-DalloIle for Fmoc-DIle, Fmoc-Ser(tBu) for Fmoc-Thr(tBu), and Fmoc-Thr(tBu) for Fmoc-Nva. After cleavage of the peptide from the resin using (95:5) TFA/water solution and work-up, the crude product was purified by HPLC using C-18 column and eluting with a solvent mixture varying in a gradient from 5% to 100% acetonitrile/water containing 0.01% TFA over a period of 50 min. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-

DalloIle-Ser-Thr-Ile-Arg-ProNHEt as the trifluoroacetate salt: $R_t = 3.089$ min (10% to 40% acetonitrile in water containing 0.01% of TFA, over 30 min period); MS (ESI) m/e 982 ($M+H$)⁺; Amino Acid Anal.: 0.95 Sar; 0.96 Gly; 0.99 Val; 1.06 alloIle; 0.97 Ile; 0.57 Thr; 0.31 Ser; 1.02 Arg; 1.02 Pro.

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Example 366

N-Ac-Sar-Gly-Gln-DIle-Thr-Nva-DIle-Arg-ProNHEt

The procedure described in example 1 was used but substituting Fmoc-Gln(Trt) for Fmoc-Val and Fmoc-DIle for Fmoc-Ile. After cleavage of the peptide from the resin using (95:5) TFA/water solution and work-up, the crude product was purified by HPLC using C-18 column and eluting with a solvent mixture varying in a gradient from 5% to 100% acetonitrile/water containing 0.01% TFA over a period of 50 min. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Gln-DIle-Thr-Nva-DIle-Arg-ProNHEt as the trifluoroacetate salt: $R_t = 2.89$ min (10% to 40% acetonitrile in water containing 0.01% of TFA, over 30 min period); MS (ESI) m/e 1023 ($M+H$)⁺; Amino Acid Anal.: 1.00 Sar; 0.97 Gly; 0.93 Glu; 2.15 Ile; 0.57 Thr; 1.02 Nva; 1.11 Arg; 1.10 Pro.

Example 367

N-Ac-Sar-Gly-Asn-DIle-Thr-Nva-Lys(Ac)-Arg-ProNHEt

The procedure described in example 1 was used but substituting Fmoc-Asn(Trt) for Fmoc-Val, and Fmoc-Lys(Ac) for Fmoc-Ile. After cleavage of the peptide from the resin using (95:5) TFA/water solution and work-up, the crude product was purified by HPLC using C-18 column and eluting with a solvent mixture varying in a gradient from 5% to 100% acetonitrile/water containing 0.01% TFA over a period of 50 min. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Asn-DIle-Thr-Nva-Lys(Ac)-Arg-ProNHEt as the trifluoroacetate salt: $R_t = 4.58$ min (10% to 40% acetonitrile in water containing 0.01% of TFA, over 30 min period); MS (ESI) m/e 1066 ($M+H$)⁺; Amino Acid Anal.: 0.98 Sar; 0.96 Gly; 0.92 Asp; 1.01. Ile; 0.52 Thr; 1.04 Nva; 1.03 Lys; 0.95 Arg; 1.06 Pro.

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Example 368

N-Ac-Sar-Gly-Gln-DalloIle-Tyr-Nva-DIle-Arg-ProNHEt

The procedure described in example 366 was used but substituting Fmoc-DalloIle for Fmoc-DIle, and Fmoc-Tyr(tBu) for Fmoc-Thr(tBu). After cleavage of the peptide from the resin using (95:5) TFA/water solution and work-up, the crude product was purified by HPLC using C-18 column and eluting with a solvent mixture varying in a gradient from

5% to 100% acetonitrile/water containing 0.01% TFA over a period of 50 min. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Gln-DalloIle-Tyr-Nva-DIle-Arg-ProNHEt as the trifluoroacetate salt: $R_t = 3.357$ min (10% to 40% acetonitrile in water containing 0.01% of TFA, over 30 min period); MS (ESI) m/e 1085 ($M+H^+$); Amino Acid Anal.: 0.93 Sar; 0.97 Gly; 0.99 Glu; 2.07 Ile; 0.93 Tyr; 1.01 Nva; 0.97 Arg; 1.00 Pro.

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Example 369

N-Ac-Sar-Gly-Gln-DalloIle-Thr-Nva-Ile-Arg-Pro-DAlaNH₂

The procedure described in example 357 was used but substituting Fmoc-DalloIle
10 for Fmoc-DIle. After cleavage of the peptide from the resin using (95:5) TFA/water solution and work-up, the crude product was purified by HPLC using C-18 column and eluting with a solvent mixture varying in a gradient from 5% to 100% acetonitrile/water containing 0.01% TFA over a period of 50 min. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Gln-DalloIle-Thr-Nva-Ile-Arg-Pro-DAlaNH₂ as the trifluoroacetate salt: $R_t = 2.38$ min (10% to 40% acetonitrile in water containing 0.01% of TFA, over 30 min period); MS (ESI) m/e 1066 ($M+H^+$); Amino Acid Anal.: 0.99 Sar; 1.00. Gly; 0.83 Glu; 2.03 Ile; 0.47 Thr; 1.02 Nva; 1.05 Arg; 1.03 Pro; 1.03 Ala.

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Example 370

N-Ac-Sar-Gly-Asn-DLeu-Thr-Ser-Ile-Arg-ProNHEt

The procedure described in example 362 was used but substituting Fmoc-Thr(tBu)
for Fmoc-Ser(tBu) and Fmoc-Ser(tBu) for Fmoc-Nva. After cleavage of the peptide from
the resin using (95:5) TFA/water solution and work-up, the crude product was purified by
HPLC using C-18 column and eluting with a solvent mixture varying in a gradient from
25 5% to 100% acetonitrile/water containing 0.01% TFA over a period of 50 min. The pure
fractions were lyophilized to yield N-Ac-Sar-Gly-Asn-DLeu-Thr-Ser-Ile-Arg-ProNHEt as
the trifluoroacetate salt: $R_t = 2.375$ min (10% to 40% acetonitrile in water containing
0.01% of TFA, over 30 min period); MS (ESI) m/e 997 ($M+H^+$); Amino Acid Anal.: 0.93
Sar; 0.98 Gly; 0.96 Asp; 1.03 Leu; 0.54 Thr; 0.21 Ser; 0.97 Ile; 1.01 Arg; 1.06 Pro.

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Example 371

N-Ac-Sar-Gly-Val-DIle-alloThr-Ser-Ile-Arg-ProNHEt

The procedure described in example 360 was used but substituting Fmoc-Ser(tBu)
for Fmoc-Nva. After cleavage of the peptide from the resin using (95:5) TFA/water
35 solution and work-up, the crude product was purified by HPLC using C-18 column and
eluting with a solvent mixture varying in a gradient from 5% to 100% acetonitrile/water

containing 0.01% TFA over a period of 50 min. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-DIle-alloThr-Ser-Ile-Arg-ProNHEt as the trifluoroacetate salt: R_t = 3.104 min (10% to 40% acetonitrile in water containing 0.01% of TFA, over 30 min period); MS (ESI) m/e 982 (M+H)⁺; Amino Acid Anal.: 0.97 Sar; 1.00 Gly; 0.71 Val; 1.64 Ile; 0.54 Thr; 0.20 Ser; 1.08 Arg; 1.02 Pro.

5 Example 372

N-Ac-Sar-Gly-Gln-DIle-alloThr-Nva-Ile-Arg-ProNHEt

The procedure described in example 360 was used but substituting Fmoc-Gln(Trt) for Fmoc-Val. After cleavage of the peptide from the resin using (95:5) TFA/water solution and work-up, the crude product was purified by HPLC using C-18 column and eluting with a solvent mixture varying in a gradient from 5% to 100% acetonitrile/water containing 0.01% TFA over a period of 50 min. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Gln-DIle-alloThr-Nva-Ile-Arg-ProNHEt as the trifluoroacetate salt: R_t = 2.835 min (10% to 40% acetonitrile in water containing 0.01% of TFA, over 30 min period); MS (ESI) m/e 1023 (M+H)⁺; Amino Acid Anal.: 0.98 Sar; 0.99 Gly; 1.05 Glu; 1.93 Ile; 0.64 Thr; 0.92 Nva; 1.12 Arg; 1.12 Pro.

20 Example 373

N-Ac-Sar-Gly-Val-DIle-alloThr-Nva-Pro-Arg-ProNHEt

The procedure described in example 360 was used but substituting Fmoc-Pro for Fmoc-Ile. After cleavage of the peptide from the resin using (95:5) TFA/water solution and work-up, the crude product was purified by HPLC using C-18 column and eluting with a solvent mixture varying in a gradient from 5% to 100% acetonitrile/water containing 0.01% TFA over a period of 50 min. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-DIle-alloThr-Nva-Pro-Arg-ProNHEt as the trifluoroacetate salt: R_t = 3.149 min (10% to 40% acetonitrile in water containing 0.01% of TFA, over 30 min period); MS (ESI) m/e 978 (M+H)⁺; Amino Acid Anal.: 0.90 Sar; 0.99 Gly; 1.03 Glu; 0.89 Ile; 0.59 Thr; 0.85 Nva; 1.16 Arg; 2.14 Pro.

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Example 374

N-Ac-Sar-Gly-Val-DalloIle-Thr-Trp-Ile-Arg-ProNHEt

The procedure described in example 13 was used but substituting Fmoc-Trp(Boc) for Fmoc-Nva. After cleavage of the peptide from the resin using (95:5) TFA/water solution and work-up, the crude product was purified by HPLC using C-18 column and eluting with a solvent mixture varying in a gradient from 5% to 100% acetonitrile/water

containing 0.01% TFA over a period of 50 min. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-DalloIle-Thr-Trp-Ile-Arg-ProNHEt as the trifluoroacetate salt: R_t = 4.203 min (10% to 40% acetonitrile in water containing 0.01% of TFA, over 30 min period); MS (ESI) m/e 1081 (M+H)⁺; Amino Acid Anal.: 0.91 Sar; 0.96 Gly; 0.99 Val; 5 1.04 alloIle; 0.61 Thr; 0.21 Trp; 1.03 Arg; 1.03 Pro.

Example 375

N-Ac-Sar-Gly-Val-DalloIle-Ser-Ser-Ile-Arg-ProNHCH(CH₃)₂

The procedure described in example 4 was used but substituting Fmoc-Ser(tBu) for both Fmoc-Thr(tBu) and Fmoc-Nva. After cleavage of the peptide from the resin using (95:5) TFA/water solution and work-up, the crude product was purified by HPLC using C-18 column and eluting with a solvent mixture varying in a gradient from 5% to 100% acetonitrile/water containing 0.01% TFA over a period of 50 min. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-DalloIle-Ser-Ser-Ile-Arg-ProNHCH₂(CH₃)₂ as the trifluoroacetate salt: R_t = 2.88 min (10% to 40% acetonitrile in water containing 0.01% of TFA, over 30 min period); MS (ESI) m/e 982 (M+H)⁺; Amino Acid Anal.: 1.03 Sar; 0.97 Gly; 0.99 Val; 2.04 Ile; 0.78 Ser; 1.00 Arg; 1.06 Pro.

Example 376

N-Ac-Sar-Gly-Val-DIle-Thr-Gln-DIle-Arg-ProNHCH₂CH₃

The procedure described in example 43 was used but substituting Fmoc-DIle for Fmoc-Ile. After cleavage of the peptide from the resin using (95:5) TFA/water solution and work-up, the crude product was purified by HPLC using C-18 column and eluting with a solvent mixture varying in a gradient from 5% to 100% acetonitrile/water containing 0.01% TFA over a period of 50 min. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-DIle-Thr-Gln-DIle-Arg-ProNHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.01 min (10% to 40% acetonitrile in water containing 0.01% of TFA, over 30 min period); MS (ESI) m/e 1023 (M+H)⁺; Amino Acid Anal.: 1.00 Sar; 1.02 Gly; 1.03 Val; 2.11 Ile; 0.49 Thr; 0.92 Glu; 0.93 Arg; 1.04 Pro.

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Example 377

N-Ac-Sar-Gly-Val-DalloIle-Thr-Trp-DIle-Arg-ProNHEt

The procedure described in example 374 was used but substituting Fmoc-DIle for Fmoc-Ile. After cleavage of the peptide from the resin using (95:5) TFA/water solution and work-up, the crude product was purified by HPLC using C-18 column and eluting with a solvent mixture varying in a gradient from 5% to 100% acetonitrile/water

containing 0.01% TFA over a period of 50 min. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-DalloIle-Thr-Trp-DIle-Arg-ProNHEt as the trifluoroacetate salt: R_t = 4.44 min (10% to 40% acetonitrile in water containing 0.01% of TFA, over 30 min period); MS (ESI) m/e 1081 (M+H)⁺; Amino Acid Anal.: 1.05 Sar; 0.97 Gly; 0.96 Val; 5 2.05 Ile; 0.51 Thr; 0.28 Trp; 1.07 Arg; 1.09 Pro.

Example 378

N-Ac-Sar-Gly-Val-DalloIle-Thr-Nva-Ile-Arg-DProNHEt

The procedure described in example 14 was used but substituting Fmoc-DPro-10 Sieber ethylamide for Fmoc-Pro-Sieber ethylamide. After cleavage of the peptide from the resin using (95:5) TFA/water solution and work-up, the crude product was purified by HPLC using C-18 column and eluting with a solvent mixture varying in a gradient from 5% to 100% acetonitrile/water containing 0.01% TFA over a period of 50 min. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-DalloIle-Thr-Nva-Ile-Arg-15 DProNHEt as the trifluoroacetate salt: R_t = 3.52 min (10% to 40% acetonitrile in water containing 0.01% of TFA, over 30 min period); MS (ESI) m/e 994 (M+H)⁺; Amino Acid Anal.: 1.00 Sar; 1.02 Gly; 1.01 Val; 2.10 Ile; 0.55 Thr; 0.99 Nva; 0.92 Arg; 1.01 Pro.

Example 379

N-Ac-Sar-Gly-Val-DIle-Met-Nva-Ile-Arg-Pro-DAlaNH₂

The procedure described in example 75 was used but substituting Fmoc-Met for Fmoc-Thr(tBu). After cleavage of the peptide from the resin using (95:5) TFA/water solution and work-up, the crude product was purified by HPLC using C-18 column and eluting with a solvent mixture varying in a gradient from 5% to 100% acetonitrile/water 20 containing 0.01% TFA over a period of 50 min. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-DIle-Met-Nva-Ile-Arg-Pro-DAlaNH₂ as the trifluoroacetate salt: R_t = 4.05 min (10% to 40% acetonitrile in water containing 0.01% of TFA, over 30 min 25 period); MS (ESI) m/e 1067 (M+H)⁺; Amino Acid Anal.: 0.92 Sar; 0.96 Gly; 1.03 Val; 2.05 Ile; 0.91 Met; 1.05 Nva; 1.03 Arg; 1.02 Pro.

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Example 380

N-Ac-Sar-Gly-Val-DIle-alloThr-Pro-Ile-Arg-Pro-NHCH₂CH₃

The procedure described in example 60 was used but substituting Fmoc-Pro for Fmoc-Nva. After cleavage of the peptide from the resin using (95:5) TFA/water solution 35 and work-up, the crude product was purified by HPLC using C-18 column and eluting with a solvent mixture varying in a gradient from 5% to 100% acetonitrile/water

containing 0.01% TFA over a period of 50 min. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-DIle-alloThr-Nva-Pro-Arg-Pro-NHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.551 min (10% to 40% acetonitrile in water containing 0.01% of TFA, over 30 min period); MS (ESI) m/e 992 (M+H)⁺; Amino Acid Anal.: 0.95 Sar; 0.97 Gly; 0.99 Val; 5 1.96 Ile; 0.97 Arg; 2.08 Pro.

Example 381

N-Ac-Sar-Gly-Val-DalloIle-alloThr-Gln-Ile-Arg-Pro-NHCH₂CH₃

The procedure described in example 380 was used but substituting Fmoc-alloIle 10 for Fmoc-DIle, Fmoc-Gln(Trt) for Fmoc-Pro. After cleavage of the peptide from the resin using (95:5) TFA/water solution and work-up, the crude product was purified by HPLC using C-18 column and eluting with a solvent mixture varying in a gradient from 5% to 100% acetonitrile/water containing 0.01% TFA over a period of 50 min. The pure 15 fractions were lyophilized to yield N-Ac-Sar-Gly-Val-DalloIle-alloThr-Gln-Ile-Arg-Pro-NHCH₂CH₃ as the trifluoroacetate salt: R_t = 3.08 min (10% to 40% acetonitrile in water containing 0.01% of TFA, over 30 min period); MS (ESI) m/e 1023 (M+H)⁺; Amino Acid Anal.: 0.95 Sar; 0.91 Gly; 1.00 Val; 2.02 Ile; 0.98 Glu; 1.01 Arg; 1.05 Pro.

Example 382

N-Ac-Sar-Gly-Val-DalloIle-Ser-Ser-Ile-Arg-Pro-DAlaNH₂

The procedure described in example 75 was used but substituting Fmoc-DalloIle 20 for Fmoc-DIle, Fmoc-Ser(tBu) for both Fmoc-Thr(tBu) and Fmoc-Nva. After cleavage of the peptide from the resin using (95:5) TFA/water solution and work-up, the crude product was purified by HPLC using C-18 column and eluting with a solvent mixture varying in a 25 gradient from 5% to 100% acetonitrile/water containing 0.01% TFA over a period of 50 min. The pure fractions were lyophilized to yield N-Ac-Sar-Gly-Val-DalloIle-Ser-Ser-Ile-Arg-Pro-DAlaNH₂ as the trifluoroacetate salt: R_t = 2.80 min (10% to 40% acetonitrile in water containing 0.01% of TFA, over 30 min period); MS (ESI) m/e 1011 (M+H)⁺; Amino Acid Anal.: 1.04 Sar; 0.99 Gly; 0.92 Val; 1.01 alloIle; 0.44 Ser; 0.95 Arg; 1.05 Pro.

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In Vitro Assay for Angiogenic Activity

The human microvascular endothelial (HMVEC) migration assay was run according to the procedure of S. S. Tolsma, O. V. Volpert, D. J. Good, W. F. Frazier, P. J. Polverini and N. Bouck, J. Cell Biol. 122, 497-511 (1993).

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The HMVEC migration assay was carried out using Human Microvascular Endothelial Cells-Dermal (single donor) and Human Microvascular Endothelial Cells,

(neonatal). The BCE or HMVEC cells were starved overnight in DME containing 0.1% bovine serum albumin (BSA). Cells were then harvested with trypsin and resuspended in DME with 0.1% BSA at a concentration of 1.5×10^6 cells per ml. Cells were added to the bottom of a 48 well modified Boyden chamber (Nucleopore Corporation, Cabin John, MD). The chamber was assembled and inverted, and cells were allowed to attach for 2 hours at 37 °C to polycarbonate chemotaxis membranes (5 µm pore size) that had been soaked in 0.1% gelatin overnight and dried. The chamber was then reinverted, and test substances (total volume of 50 µl), including activators, 15 ng/ml bFGF/VEGF, were added to the wells of the upper chamber. The apparatus was incubated for 4 hours at 37 °C. Membranes were recovered, fixed and stained (Diff Quick, Fisher Scientific) and the number of cells that had migrated to the upper chamber per 3 high power fields counted. Background migration to DME + 0.1 BSA was subtracted and the data reported as the number of cells migrated per 10 high power fields (400X) or, when results from multiple experiments were combined, as the percent inhibition of migration compared to a positive control.

Representative compounds inhibited human endothelial cell migration in the above assay at the percentages and concentrations shown in Tables 3 and 4.

Table 3
In Vitro Angiogenic Activity

<u>Ex. #</u>	<u>% Inhib. @ 20 nM</u>	<u>% Inhib. @ 10 nM</u>
1	87.3	76.9
3	56.0	---
4	71.3	---
5	---	87.2
8	---	88.2
11	70.4	---
12	55.8	---
18	---	51.4
28	---	47.0
42	60.2	---
43	---	94.1

46	77.5	---
47	69.7	---
49	83.4	---

Table 3 (continued)

<u>Ex. #</u>	<u>% Inhib.</u> <u>@ 20 nM</u>	<u>% Inhib.</u> <u>@ 10 nM</u>
50	71.6	---
51	67.0	---
52	46.5	---
53	76.7	---
54	81.3	---
55	59.2	---
56	49.9	---
57	56.6	---
58	68.8	---
59	82.3	---
60	75.3	---
61	---	83.7
63	---	82.4
66	76.1	---

Some compounds of the instant invention had percent inhibition values of >75% at a concentration of 1 nM. Preferred compounds had percent inhibition values of >55% at a
 5 concentration of 0.1 nM, and most preferred compounds had percent inhibition values of >70% at a concentration of 0.1 nM.